EPIDEMIOLOGY OF, AND MEASUREMENT APPROACHES TO, CHRONIC RHINOSINUSITIS AND NASAL AND SINUS SYMPTOMS: EXACERBATIONS, WORKPLACE IMPACTS, AND RADIOLOGIC INFLAMMATION

by

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Abstract

Background: Chronic rhinosinusitis (CRS) is a prevalent upper respiratory condition characterized by inflammation of the paranasal sinuses. Few epidemiologic studies of CRS have been performed outside of tertiary care settings (e.g., surgical referral centers), likely representing the most severe end of the disease spectrum.

Objectives: 1) compare several definitions of acute exacerbations of nasal and sinus symptoms (AENSS) by prevalence and risk factors; 2) quantify the workplace indirect costs of CRS, related conditions, and nasal and sinus and related symptoms; and 3) investigate measurement properties of two commonly used sinus computed tomography (CT) opacification scoring procedures (Lund-Mackay [LM] and modified Lund-Mackay [mLM]).

Methods: We selected individuals from the electronic health record (EHR) of Geisinger to participate in a longitudinal questionnaire-based study of CRS. Of the 23,700 individuals selected from the EHR, 7847 responded to the baseline questionnaire. Self-reported NSS and physician diagnoses were used to operationalize AENSS. Measures of workplace absenteeism, presenteeism, and lost productive time (LPT) were derived from responses based on the Work and Health Interview. Sinus CT scans were completed for a subset of 646 individuals and opacification was quantified by LM and mLM. Measurement properties were assessed by EFA and further characterized by LCA for LM only.

Results: AENSS were common in the general population with seasonal trends in exacerbation dependent on operationalization. AENSS based on timing of symptoms and worsening mucopurulence (AENSS-Sx-Pur) had risk factors consistent with literature and less seasonal trends in prevalence. Workplace LPT was driven by three symptom domains: pain and pressure, nasal blockage and discharge, and asthma and

constitutional symptoms, which mediated the associations of diagnoses with LPT. Lastly, LM and mLM appeared to measure the same underlying construct (i.e. sinus inflammation). However, latent class analysis (LCA) identified three homogeneous subgroups of individuals based on patterns of sinus opacification.

Conclusions: AENSS was common in the general population and certain NSS domains were associated with workplace LPT. Further, single score approaches to quantifying sinus opacification are likely incorrect and location and patterns of opacification should be taken into consideration. Further studies of CRS are needed to validate these findings.

Thesis readers: Brian S. Schwartz, Karen Bandeen-Roche, Jessie P. Buckley, and Ghassan B. Hamra

Alternates: Heather E. Volk, Christopher D. Heaney, and Paul Strickland

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Chapter 1: Introduction

1.0 Rationale

Chronic rhinosinusitis (CRS) is a prevalent upper-respiratory condition of the paranasal sinuses, significantly affecting quality of life and incurring large societal burdens.[1] Few epidemiologic studies of CRS have occurred outside of the tertiary care setting; as such, our knowledge of CRS etiology, risk factors, and outcomes are limited to individuals likely comprising the most severe end of a broad spectrum of sinus disease. Therefore, the purpose of this dissertation was to perform one of the first general population-based epidemiologic studies of CRS to address critical gaps in our understanding of: 1) risk factors for exacerbations of CRS; 2) workplace impacts of CRS, comorbidities, and overlapping symptoms; and 3) measurement and correlates of radiologic inflammation in sinus disease.

1.1 Rhinosinusitis and related conditions terminology

Rhinosinusitis is a broad term used to designate conditions characterized by inflammation of the nasal cavities as well as the paranasal sinuses. It is a portmanteau created from two common medical terms: *rhino* (meaning “of the nose”) and *sinus*, with the suffix -*itis* indicating inflammation. Below, we introduce and define several related conditions characterized by rhinosinusitis.

1.1.1 Acute rhinosinusitis

Acute rhinosinusitis (ARS) is defined by several consensus groups, including the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS),[1] the American Academy of Otolaryngology–Head and Neck Surgery (AAO–HNS),[2] and the International Consensus Statement on Allergy and Rhinology (ICAR)[3] by presence of the following symptoms: nasal blockage, congestion, or stuffiness; nasal discharge or postnasal drip (could be mucopurulent); reduction (hyposmia) or loss of smell (anosmia); and facial pain or pressure.[1,2] Importantly, at least one of the first two nasal symptoms must be

present and there must be at least two symptoms total.[1] While symptomatology requirements are the same across consensus groups, they differ in establishing which durations are indicative of ARS with EPOS using a duration of less than 12 weeks,[1] while AAO–HNS and ICAR use a duration of 4 weeks or less.[2,3]

ARS is often further sub-sectioned based on origin of inflammation (e.g., viral or bacterial) or recurrence in a defined period of time. For example, acute viral rhinosinusitis (AVRS) i.e., the common cold, generally has a symptomatic duration of less than 10 days.[1,2] Acute post-viral rhinosinusitis (APVRS) is defined by an increase in number of symptoms after five days or persistent symptoms after 10 days, with symptoms not lasting beyond 12 weeks.[1] Acute bacterial rhinosinusitis (ABRS) is defined differently by EPOS and AAO–HNS, though both agree that inflammation is of bacterial origin.[1,2] EPOS defines ABRS as any combination of three or more symptoms or signs of: discolored discharge (with unilateral predominance) and purulent secretion in the *casum navi* (nasal cavity); severe local pain (with unilateral predominance); fever (>38°C or 100.4°F); elevated erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP); and, “double-sickening” which is a worsening of symptoms after an initial improvement or mild phase of symptoms.[1] AAO–HNS, however, defines ABRS by ARS with suspected or confirmed bacterial infection in the nasal cavity or paranasal sinuses and either persistence or worsening of symptoms after 10 days.[2] Lastly, recurrent ARS (RARS) is defined as ARS episodes occurring at least four times per year with complete remission of symptoms between episodes.[2,3]

1.1.2 Chronic rhinosinusitis

Several consensus groups define chronic rhinosinusitis (CRS) by subjective symptoms and objective evidence, both of which are required to clinically diagnose an individual (CRS_C).[1] The subjective symptoms component is the same as for ARS;

however, these symptoms must have a duration of at least 12 weeks.[1-3] Objective evidence, used to confirm the subjective symptoms, includes: endoscopic confirmation of nasal polyps, mucopurulent discharge of the middle meatus, and/or edema with or without mucosal obstruction in the middle meatus; and/or computed tomography (CT) scans of the osteomeatal complex and sinuses.[1-3] EPOS proposed a definition for epidemiologic research based solely on the aforementioned subjective symptoms (CRS_S) and duration criteria, since objective evidence is often difficult to obtain in large-scale studies.[1] However, other operationalizations of CRS definitions exist, including those based on: objective evidence only (CRS_O); International Classification of Diseases (ICD) codes in medical records (CRS_{ICD}); electronic health records (EHR; CRS_{EHR}), extending CRS_{ICD} to also include other aspects of the EHR (e.g., current procedural terminology [CPT] codes and laboratory diagnostics); and self-reported physician diagnosis of CRS (CRS_{SR}).

Throughout this dissertation, we make note of which definition of CRS is being described, saving the general use of "CRS" (with no clarifying subscript) for broad discussions of the underlying disease.

1.1.3 Related conditions

1.1.3.1 *Allergic and non-allergic rhinitis*

Rhinitis, inflammation of the nasal mucosa, is differentiated by cause of symptoms onset. Allergic rhinitis (often referred to as "hay fever") is characterized by an immunoglobulin E (IgE)-mediated immune response to external stimuli (e.g., animal dander, fungi, pollens) interacting with nasal mucosa.[4,5] This atopic sensitization to certain external stimuli represents the hallmark of allergic responses in general; however, in allergic rhinitis this results in symptoms of: itching (nasal or ocular [i.e. eye]), rhinorrhea (runny nose), nasal discharge, epiphora (watering eyes), and sneezing.[4,5]

Non-allergic rhinitis, while encompassing the same set of symptoms, is distinct from allergic rhinitis because the symptoms are not induced by an atopic response to external stimuli.[6] Instead, symptoms are induced by a combination of biologic pathways, including: classic inflammatory, neurogenic, and idiopathic (unknown).[7]

1.1.3.2 *Asthma*

Asthma is a heterogeneous chronic inflammatory condition of the lower airways characterized by diverse and recurrent symptoms (e.g., wheeze, shortness of breath, chest tightness), airflow obstruction, and bronchial hyperresponsiveness.[8]

1.1.3.3 *Aspirin exacerbated respiratory disease/Samter's triad*

Aspirin exacerbated respiratory disease (AERD), sometimes referred to as Samter's triad, is a culmination of three distinct conditions, including: nasal polyposis, aspirin (and other cyclooxygenase 1 [COX-1] inhibitors) allergy, and asthma.[9]

1.1.3.4 *Acute exacerbation of chronic rhinosinusitis*

Acute exacerbation of chronic rhinosinusitis (AECRS), sometimes referred to as "acute on chronic" CRS, is a sudden worsening of CRS-relevant nasal and sinus symptoms (NSS). While closely related to ARS, AECRS is not believed to simply be a viral cold in someone with CRS, but rather a separate pathologic phenomenon. The difficulty in formally defining AECRS stems from the fact that no universal or consensus-recognized definition exists. To date, only 13 studies of AECRS have been completed, nearly all using a different operationalized definition. A summary of the studies, their respective samples, definitions, and conclusions is provided in **Table 1.1.3.4.1**. The majority of the few existing AECRS studies have focused on medical interventions and treatments, microbiology, or immunology of—as opposed to understanding the broad set of risk factors for—AECRS. As such, ICAR has declared a need for more extensive prospective studies analyzing AECRS, especially in general population samples, to

better understand and define this phenomenon. The first aim of this dissertation was a direct response to this call-to-action.

Table 1.1.3.4.1. Overview of prior studies of acute exacerbations of CRS (AECRS)

Study	Study Population	Study Design	Study Period	Sample Size, N	AECRS Definition	Primary Objective	Authors Conclusion(s)
Bhattacharyya and Kepnes (1999)	Cultures from patients who had undergone ESS[a]	Retrospective case series	Jan. 1, 1994 - Dec. 31, 1998	290 cultures from 125 patients	Presence of ≥1 major or minor symptom of CRS[b] + mucopurulent secretions which were predominantly gram-positive cocci	Evaluate the microbiology of CRS patients after ESS	An array of bacteria, including *Pseudomonas*, are present in patients following ESS
Brook et al. (2005)	Cultures from patients with CRS exacerbation	Retrospective case series	June 1991 - Sept. 1999	22 aspirates from 7 patients	Presence of the following criteria: meet clinical definition of CRS, suffer from chronic maxillary sinusitis, exhibit significant acute aggravation of sinusitis symptoms (7-30 days), and have bacteria isolated from sinus cultures. Sinusitis was defined radiographically by sinus opacity, air-fluid level, or mucous membrane thickening of at least 6mm in the maxillary sinus.	Evaluate the microbiology of acute exacerbation of chronic sinusitis	Bacteria isolated from patients with an exacerbation were largely anaerobic

Study	Study Population	Study Design	Study Period	Sample Size, N	AECRS Definition	Primary Objective	Authors Conclusion(s)
Brook (2006)	Cultures from patients with CRS exacerbation	Retrospective case series	June 1987 - June 2004	89 cultures from 30 patients	Presence of following criteria: maxillary sinusitis, exhibition of significant acute aggravation of sinusitis symptoms (lasting >30 days), and bacterial cultures isolated from sinuses	Evaluate the microbiology of acute exacerbation of chronic sinusitis	Bacteria isolated from patients with an exacerbation were largely anaerobic
Chaudhry et al. (2006)	CRSwNP[c] patients, experiencing an acute exacerbation of symptoms	Retrospective case series	Feb. 2008 - Dec. 2012	130 patients	Presence of the following criteria: meet clinical definition of CRSwNP, increase in SNOT-22[d] score and recurrent polyposis on endoscopic examination	Determine the efficacy of TA/CMC[e] foam, as opposed to systemic corticosteroids, for controlling exacerbations of CRS in patients with previous ESS	TA/CMC foam reduced dependence on corticosteroids for treating CRS exacerbations in patients with nasal polyposis, and was well tolerated by patients

Cincik and Ferguson (2006)	Patients with CRS or subclassification of CRS, who completed an endoscopically-guided culture at the University of Pittsburgh School of Medicine	Retrospective case series	March 2004 - May 2005	27 of 77 enrolled patients	Acute rhinosinusitis symptoms (subjective and objective evidence of rhinosinusitis of <4 weeks duration) that resolve with return to baseline chronic symptoms as well as symptoms of rhinosinusitis without return to no symptoms of rhinosinusitis	Determine impact endoscopically-guided culture results had on CRS antibiotic treatment and estimate prevalence of bacterial pathogens in purulent secretions	Culture results directed changes in antibiotic therapy for the majority of patients; purulent secretions were more likely to contain bacterial pathogens than non-purulent secretions, and occurred more frequently in those with acute exacerbation of CRS
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Divekar et al. (2015)	Adult patients from two Allergy-Immunology and Otolaryngology practices in academic medical centers (Mayo Clinic Minnesota and Mayo Clinic Arizona)	Non-interventional prospective study	Fall 2012 - Spring 2013	19 patients (10 controls and 9 CRSwNP)	Presence of following criteria: meet clinical definition of CRS which is 12 weeks with at least 2 of the major criteria for diagnosis within the past 24 months; sinus CT scan within the past 5 years with a Lund-Mackay score >5; nasal polyps documented within the past 3 years on physical exam; and patient-reported worsening of sinonasal symptoms	Characterize immune responses associated with exacerbations of CRS in patients with nasal polyposis	Compared to controls, CRSwNP patients with exacerbation had elevated local secretions of IL-5[f], IL-6, MBP[g] and systemic VEGF[h] and GM-CSF[i]

Dutta and Ghatak (2013)	Adult patient attending Otorhinolaryngology clinic	Case report	N/A	1 patient	Four-day history of large, painful, bilateral erythematous periorbital swellings; nasal obstruction with purulent nasal discharge; fever; and headache	Establish connections between a CRS exacerbation with orbital complications and atrophic rhinitis	There is a temporal relationship between rhinosinusitis and atrophic rhinitis
Ikeda et al. (2011)	Patients with CRS and bronchial asthma, admitted to the Department of Otorhinolaryngology in Juntendo University Faculty of Medicine	Retrospective case series	Jan. 2006 - July 2008	75 aspirates from 42 patients	Presence of purulent sinonasal secretions in conjunction with sinus-related symptoms (e.g. nasal discharge, facial pain) in patients meeting the EPOS[j] definition of CRSwNP	Determine role of bacterial infection in co-morbid asthma and CRS patients, following ESS	Bacterial infection may be a critical factor in exacerbation of CRS and asthma, following ESS
Merkley et al. (2015)	Adult patients with CRS who had previously undergone ESS and with evidence of purulent sinonasal secretions, and were admitted to the rhinology clinic of the University of Rochester Department of Otolaryngology Head and Neck Surgery	Randomized-controlled trial	N/A	8 patients	Presence of purulent sinonasal secretions; previous ESS; diagnosis of CRS (criteria for CRS diagnosis not specified)	Evaluate response of sinus microbiome in CRS patients to antibiotics in patients experiencing exacerbation	An array of bacteria exists in CRS patients during exacerbation and after antibiotic therapy

Rank et al. (2010)	Patients with CRS in Olmsted County, MN	Retrospective cohort	2003 - 2004	1217 exacerbation visits from 800 patients	Any visit with an ICD-9[k] code of 473.xx and at least 1 of the following: prescription for systemic antibiotics and/or corticosteroid, plans for a semiurgent surgical intervention, emergency or urgent care visit, or hospitalization for CRS	Evaluate if a seasonal pattern of CRS exacerbation exists	CRS exacerbations were more common during the winter season, compared to all other seasons
Rank et al. (2013)	Adult patients with CRSwNP who had previously undergone ESS and with evidence of purulent sinonasal secretions, and were admitted to the rhinology clinic of the University of Rochester Department of Otolaryngology Head and Neck Surgery	Prospective cohort	Jan. 2012 - May 2012	10 patients	Meet clinical definition of CRS [12 weeks with at least 2 of the major criteria for diagnosis (e.g. nasal discharge, nasal obstruction), within the past 24 months; available sinus CT scan within past 5 years and Lund-Mackay score >5; documentation of nasal polyps within the past 3 years] and experience acute worsening of CRS symptoms	Use prospective measurements to determine immunological changes which occur during an exacerbation of CRS in CRSwNP patients	During exacerbation, IL-6, MBP, MPO[l], EDN[m], and uric acid were elevated in sinus secretions

Solares et al. (2006)	CRS patients with MRSA[n]-positive sinus cultures, obtained during endoscopic visualization, at the Cleveland Clinic Foundation, Head and Neck Institute	Retrospective case series	Jan. 2000 - Oct. 2003	42 MRSA-positive cultures from 24 patients	CRS patients with presence of: worsened sinus symptoms, purlence on nasal endoscopy, and positive methicillin-resistant *Staphylococcus aureus* culture	Describe use of mupirocin nasal irrigation for treatment of MRSA-related CRS exacerbation	Mupirocin nasal irrigation may evade use of antibiotics during MRSA-related CRS exacerbation
Walgama et al. (2013)	Adult CRS patients with previous ESS, experiencing exacerbation of symptoms, at the University of Texas Southwestern Medical Center	Prospective case series	March 2011 - May 2012	49 patients	CRS patients with presence of: acute exacerbation of sinonasal symptoms for ≥1 week of duration and evidence of purulent secretions from the sinus ostia or cavities, middle meatus, or sphenoethmoid recess during nasal endoscopy	Compare endoscopically-guided swabs and aspirate cultures from sinonasal sites in patients experiencing infectious CRS exacerbation following ESS	Aspirate cultures provided a higher yield culture, consisting predominantly of *Pseudomonas*

[a]Endoscopic sinus surgery; [b]chronic rhinosinusitis; [c]chronic rhinosinusitis with nasal polyps; [d]Sino-Nasal Outcome Test-22; [e]topical triamcinolone acetonide/carboxymethylcellulose; [f]interleukin; [g]maltose-binding protein; [h]vascular-endothelial growth factor; [i]granulocyte macrophage colony-stimulating factor; [j]European Position Paper on Rhinosinusitis and Nasal Polyps; [k]International Classification of Diseases; [l]myeloperoxidase; [m]eosinophil-derived endotoxin; [n]methicillin-resistant *Staphylococcus aureus*

1.2 Etiology, pathogenesis, and pathophysiology of CRS

While we did not formally assess etiology or pathogenesis of CRS as part of this dissertation, understanding the biological sequelae promulgating in observed sinus disease was important in understanding the possible risk factors for CRS. As such, we briefly introduce the etiology, pathogenesis, and pathophysiology of CRS in this section.

CRS has often been considered to manifest as two divergent phenotypes—with nasal polyps (wNP) and without nasal polyps (sNP)—with diagnosis dependent on polyp identification in the middle meatus during nasal endoscopy.[1,10] Conventionally, CRSwNP was thought to be an exaggerated atopic response while CRS_SNP was due to persistent bacterial infection[1,11]; however, recent evidence suggests that both phenotypes share common etiologic and pathogenic characteristics.[1,12-16] To better understand CRS etiology and pathogenesis, Tan et al.[17] developed a conceptual framework to help elucidate underlying mechanisms involving CRS (**Figure 1.2.1**). It has been

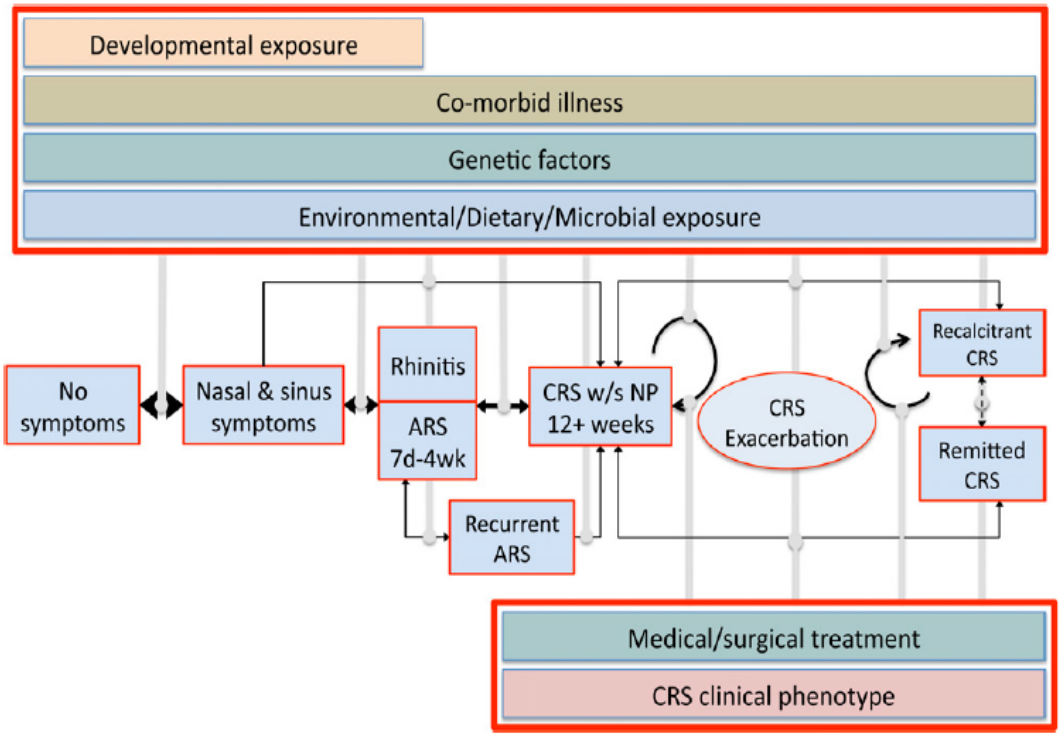

Figure 1.2.1. Rhinosinusitis framework. Adapted from: Tan et al. 2013. Chronic rhinosinusitis: the unrecognized epidemic. *Am J Respir Crit Care Med*, vol. 188(11):1275-1282.

hypothesized that CRS originates as NSS—caused (completely or partially) by a combination of previous and current exposures, co-morbidities, and genetic susceptibility—which promotes rhinitis and/or ARS, which could be recurrent (i.e. RARS).[17] Pursuant with this concept, several hypotheses regarding the origins of CRS have been articulated.

Microbes (e.g., bacteria and fungi) and deficient host-immune barriers have been proposed as causative agents in CRS development. However, no single etiologic source has been identified in all individuals diagnosed with CRS. Further, individuals have varied immunological and inflammatory responses to the same agents, thus the field of CRS research has shifted away from viewing this disease as strictly phenotypic, but rather one of many endotypes (unique subgroups of individuals identified by specific biological mechanisms or processes associated with the observed disease) culminating in the known phenotypes (CRS_SNP and CRSwNP).[7] Below, we consider each potentially causative agent or source of CRS, noting associations with specific phenotypes where available information exists. We end this section with an overview of the proposed CRS endotypes and how they relate to the various causative agents or sources as well as the major phenotypes of CRS.

1.2.1 Bacteria

The most commonly reported bacteria associated with CRS include: *Haemophilus, Moraxella, Pseudomonas, Staphylococcus aureus,* and *Streptococcus* [1,7,18]; however, *Staphylococcus aureus* is the most observed and/or elucidated.[12,19-25] To date, there are at least three major hypotheses regarding the role of bacteria in CRS development, involving superantigens, biofilms, and microbiomes.[12]

1.2.1.1 *Superantigens*

The superantigen hypothesis primarily concerns infection by *Staphylococcus* bacteria—specifically *Staphylococcus aureus* and the superantigenic exotoxin it

produces—in an effort to exaggerate local eosinophilic immune responses.[26-28] Though the presence of *S. aureus* in nasal and sinus cavities has been shown in both phenotypes of CRS,[28] the role of superantigens has been extensively implicated in the immune responses associated with CRSwNP.[26,27,29] The current understanding is that *Staphylococcus aureus* superantigens, particularly superantigen B (SEB), binds the T-cell receptor outside of the antigen-binding groove and human leukocyte antigen (HLA) major histocompatibility complex II (MHC-II), present on antigen presenting cells (APCs).[26-28] By doing so, there is a highly robust polyclonal T-cell expansion, which leads to increased pro-inflammatory cytokine release consistent with T-helper 2 cells (IL-2, IL-4, IL-5), while inhibiting T-regulatory cells and their respective cytokines (IL-10 and TGF-β), leading to a T-helper 2 dominant immune response.[27,29] This T-helper 2 biased immune response promotes immunoglobulin E (IgE) production from plasma cells (antibody secreting B-cells), which further promotes local inflammation by evoking mast cell degranulation.[30] Despite this clear eosinophilic and T-helper 2 driven inflammatory response in CRSwNP, recent evidence suggests that the immune responses are not quite so homogeneous.[1,16] In fact, studies have shown that western (Caucasian) individuals with CRSwNP tend to display the aforementioned eosinophilic/T-helper 2 responses, whereas eastern (Asian) individuals have a tendency towards a neutrophilic and T-helper 1/T-helper 17 responses.[1,16,31,32] Therefore, the utility of superantigens (and the immune responses they invoke) as an underlying mechanism for CRSwNP is debatable, and may be better described as a modifying factor or disease promoter.[12]

1.2.1.2 *Biofilms*

Biofilms, collective communities of bacteria organized within an extracellular matrix, are a survival mechanism for bacteria to resist host defense mechanisms and antibiotic treatments.[33] The presence of biofilms has been detected in both phenotypes of CRS and with greater prevalence than individuals without sinus disease,[34-38] with prevalence

dependent on detection methodology.[1,35] The specific role biofilms play in causing CRS is debatable and not fully understood.[12,39,40]

1.2.1.3 *Microbiomes*

Similarly, the role of the nasal and sinus microbiomes has been the topic of recent research in CRS. Results from prior studies have been incredibly divergent, with no clear associations between microbiome diversity and richness/abundance with either phenotype. The clearest observation across relevant studies is that bacterial diversity in the sinonasal microbiome is reduced when *Staphylococcus aureus* is abundant, with the latter bacteria often observed in individuals with CRSwNP.[41-46] However, inconsistent use of sensitive molecular techniques (e.g., 16s RNA), differences in sampling locations, and difficulties in extracting samples from the target areas (e.g., from within sinus rather than from nasal cavity without contamination from the latter), makes this concept an issue of much needed advancement.[12]

1.2.2 Fungi

The role of fungi in CRS has been an issue of initial acclaim and subsequent dismissal.[12] Early studies evaluating the role of fungal infections in CRS development found nearly all subjects with active CRS were predominantly colonized with *Alternaria* fungi, with colonization either absent in controls[47] or in reduced concentration.[48] However, later studies, including a double-blind randomized controlled trial, found little efficacy of antifungals in treating CRS.[49,50] Even if fungal infections are not the primary etiologic cause of CRS, however, they are thought to be important in characterizing individuals who transition from allergic fungal rhinosinusitis (AFRS) to CRS[17] with *Alternaria* and *Aspergillus* being most often implicated.[1,47,51]

1.2.3 Immune barriers:

Lastly, a concept which seeks to support each of the aforementioned hypotheses has been recently developed, involving deficiencies in immune barriers.[12] In brief,

exposures to foreign materials are generally handled via mucociliary clearance with no subsequent ensuing illness; however, inadequate mucociliary clearance and mechanical barriers (e.g. tight junctions) results in increased biologically relevant contact with these various foreign agents, resulting in inflammation, inadequate host responses, and ultimately sinus disease.[52-54] It is also believed that imbalances in innate antimicrobials (defensins, lysozymes, S100s, lactoferrin, complement, collectins),[1] altered pattern recognition receptor (PRR) signaling,[12] and (most recently) defective T2R bitter taste receptors in the nose[55] may play a role in CRS etiology.

1.2.4 Endotypes of CRS

As previously mentioned, the field of CRS research has shifted away from viewing this disease as strictly phenotypic. Several recent studies have attempted to identify endotypes of CRS, though few are consistent across studies, and none were completed using individuals from a general population-based sample. A joint consensus group of the European Academy of Allergy and Clinical Immunology (EAACI) and American Academy of Allergy, Asthma & Immunology (AAAAI) outlined a potential framework for associating phenotypes of CRS with endotypes (**Figure 1.2.4.1**).[7] However, the development of CRS is likely more multifactorial than the proposed framework suggests.

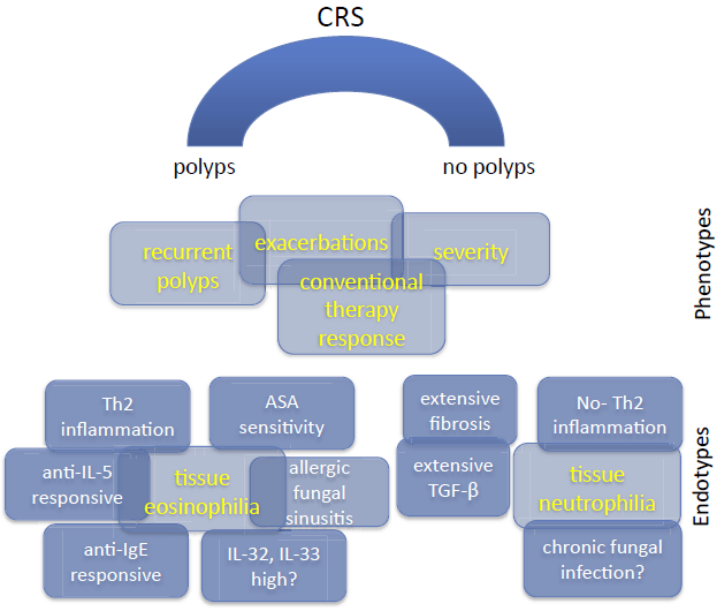

Figure 1.2.4.1. Key phenotypes and proposed endotypes of CRS and their possible associations. *ASA*, aspirin; *CRS*, chronic rhinosinusitis; *IL*, interleukin; *IgE*, immunoglobulin E; *Th*, T-helper. Akdis et al. 2013. Endotypes and phenotypes of chronic rhinosinusitis: a PRACTALL document of the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma & Immunology. *J Allergy Clin Immunol*. 131:1479-14790.

Several studies have identified chemokines (namely CCL-18[56] and CCL-23[57]), proteins which are chemotactic (engender movement and recruitment of neighboring cells) and bring inflammatory cells to target sites in tissue,[58] as potentially important biomarkers in (western) nasal polyposis (CRSwNP).[56,57] Similarly, a prior study of participants with CRSwNP, CRS_SNP, and AERD found several T-helper (Th)-2 cytokines (proteins secreted by cells[59]) were associated with CRSwNP and AERD, but no differences were observed for CRS_SNP.[60] Specifically, increased levels of interleukin (IL)-5, IL-13, eotaxin-2, and monocyte chemoattractant protein (MCP)-4 were associated with CRSwNP while increased levels of eosinophil cationic protein (ECP), granulocyte macrophage-colony stimulating factor (GM-CSF), and MCP-1 were associated with AERD. Decreased expression of tissue plasminogen activator (tPA) was also associated with AERD.[60]

In the same vein, a multi-center study identified as many as 10 endotypes represented by participants with CRS_SNP, CRSwNP, and controls (individuals undergoing sinus surgery but who did not have diagnosis of CRS).[61] This study observed IL-5 to be a key component in broadly differentiating two classes of endotypes,

with low IL-5 levels identifying four endotypes: three representing CRS_SNP with low prevalence of comorbid asthma and one representing a Th17 with a mix of CRS_SNP and CRSwNP phenotypes. The remaining six endotypes were further differentiated based on medium or high IL-5 levels, comorbid asthma prevalence, and *Staphylococcus aureus* enterotoxin-specific IgE.[61]

While an endotype-driven approach to classification (and certainly treatment) of CRS is useful in accounting for the high variability in inflammation profiles represented by this one condition, no studies have replicated findings or found consistent endotypes across geographies and racial/ethnic groups.[62]

1.3 Epidemiology of CRS

1.3.1 Estimates of prevalence and risk

Although CRS has been diagnosed in children,[1,10,63,64] the majority of cases and epidemiologic research are from adults.[1] Several studies have attempted to assess the prevalence of CRS across multiple countries; however, the shared symptoms between CRS and other conditions (e.g. acute rhinosinusitis, allergic rhinitis, and migraine headache) makes differential diagnosis difficult without objective evidence of inflammation.[17] We detail prior epidemiologic studies of CRS, noting the definition used in the study (e.g., CRS_S, CRS_O, CRS_C), to aid in comparisons.

A 1996 study in Korea estimated the prevalence of CRS_C to be 1.0%, which is the lowest prevalence of CRS estimated across all definitions.[65] A recent study in Europe, using a sample of participants with indication for CT scans of the sinuses (but did not have prior diagnosis of CRS), estimated the prevalence of CRS_C to be 3.0%.[66]

Studies of CRS_O have most frequently utilized participants receiving sinus surgery or had a clinical indication (other than CRS) requiring CT or nasal endoscopy.[66-68] It is difficult to compare across these studies because of a range of selection bias issues for

studied participants across studies and different methods of ascertaining and quantifying objective evidence were used for each. One study assessed CT scans of the sinuses to estimate the prevalence of "abnormal" sinuses (including mucosal thickening, polyps, opacification, and bone destruction) among non-CRS participants (but had other indication for CT), finding 42.5% of participants had at least one abnormality in one of the sinuses.[67] Another study, using a sample of participants undergoing sinus surgery for CRS, found a prevalence of 79% for CRS_O. The most recent study estimated a prevalence of 14% using a sample of participants with indication for CT scans, but did not have a prior diagnosis of CRS.[66]

Prevalence estimates of CRS_S are almost always considerably larger than those of CRS_C, with geographic variation in prevalence also observed. For example, population-based studies conducted in Europe and the U.S. estimated the adult prevalence of CRS_S to be 10.9%[69] and 11.9%,[70] respectively. However, a study in Brazil estimated a prevalence of 5.51%[71] while a Chinese study observed intra-county geographic variation in CRS_S prevalence, with estimates ranging from 4.8% to 9.7% (overall prevalence was 8.0%).[64]

Geographic variation is similarly observed with self-reported CRS. The frequently cited[10,17,72] 1996 National Health Interview Survey similarly estimated the prevalence of CRS_{SR} to be 12.5% of the U.S. population[73]; yet, the analogous 1996 National Population Health Survey in Canada only found a prevalence of 5.16%.[53]

Lastly, a study in Omsted, MN estimated the local prevalence of CRS_{ICD} to be 1.95%, while a recent study using primary care visits from the electronic health record (EHR) of a large health system in Pennsylvania, estimated the incidence of CRS to be 1.1 cases per 100 person-years.[74] Another study of CRS_{ICD} in this population estimated phenotype-

specific incidence rates, observing 83 CRSwNP and 1048 CRS_SNP cases per 100,000 person-years at risk.[74]

1.4 Pre- and post-morbidities associated with CRS

While we did not explicitly study the "unified airway" in this dissertation, we studied CRS and its comorbidities, including asthma and allergic rhinitis, which are comprised within the concept of unified airway disease (UAD).[75-85] Therefore, we frame this section around the UAD model. We briefly define UAD, then we describe epidemiologic evidence in support of UAD (especially as it relates to CRS) and pathogenesis of morbidities related to CRS and how they connect to CRS pathogenesis.

1.4.1 Unified airway disease

The UAD is a model of disease suggesting the upper and lower respiratory tracts are distinct regions of the same organ.[75-85] As such, conditions localized to one region (e.g., middle ear, sinuses, bronchioles) could impact physiological mechanisms in another, as long as they are both connected by the unified airway (**Figure 1.4.1.1**). Early research attempting to validate UAD have posited three major criteria to which it must account: 1) individuals with lower respiratory conditions (e.g., asthma, bronchiectasis, chronic obstructive pulmonary disease [COPD]) should have a greater risk of developing upper respiratory conditions (e.g., allergic rhinitis and CRS), and vice versa; 2) pathophysiological mechanisms within each level of the respiratory tract should explain the interactions between the two main sites; and 3) medical or surgical treatment for a

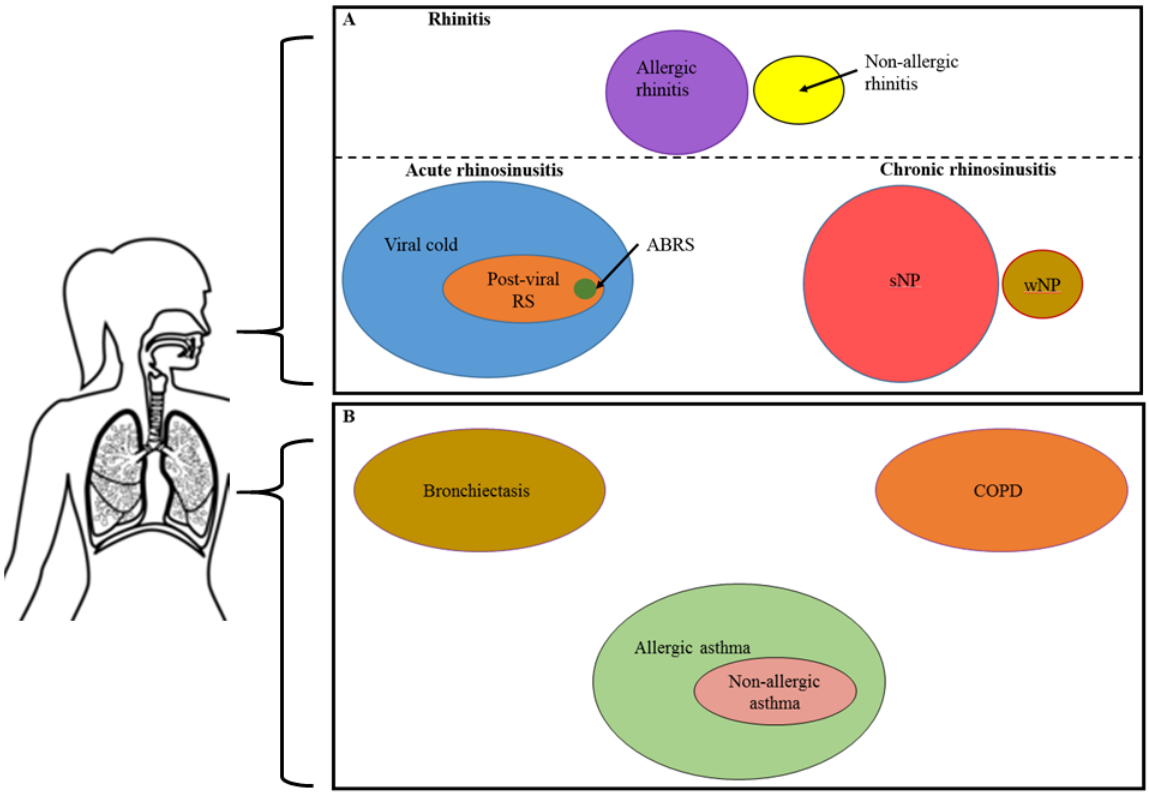

Figure 1.4.1.1. Common conditions of the (A) upper and (B) lower respiratory system. *ABRS*, acute bacterial rhinosinusitis; *COPD*, chronic obstructive pulmonary disease; *RS*, rhinosinusitis; *sNP*, without nasal polyps; *wNP*, with nasal polyps.

condition (or conditions) in one region should improve symptoms or management in the other.[77]

1.4.1.1 *Epidemiologic evidence for UAD*

Several studies have provided evidence supporting the first criterion.[9,70,74,83,86-98] For example, a prior study of CRS_{ICD} found several pre-morbid conditions were associated with increased risk of incident CRS_{ICD} (**Figure 1.4.1.1.1**).[74] Conditions suggestive of the UAD, specifically acute sinusitis (i.e. ARS), otitis media (i.e. ear infection), allergic rhinitis, asthma, pneumonia (i.e. infection in the lungs), and gastroesophageal reflux disease (GERD), conferred increased risk of CRS_{ICD} in both phenotypes ($CRS_{S}NP$ and CRSwNP). Another study in the same source population observed incident cases of CRS_{ICD} were associated with increased hazard of subsequently developing upper

respiratory conditions – ARS, otitis media, acute upper respiratory infection (URI), allergic rhinitis – as well as lower respiratory conditions – asthma, COPD, GERD, and pneumonia (**Figure 1.4.1.1.2**).[98]

Yet another study in the same source population similarly observed current CRS_S was associated with increased odds of self-reported physician diagnoses of asthma and allergic rhinitis as well as migraine headaches.[70] Comparable findings were also observed in two European population-based epidemiologic studies of CRS_S, as part of the Global Allergy and Asthma European Network (GA^2LEN).[99,100]

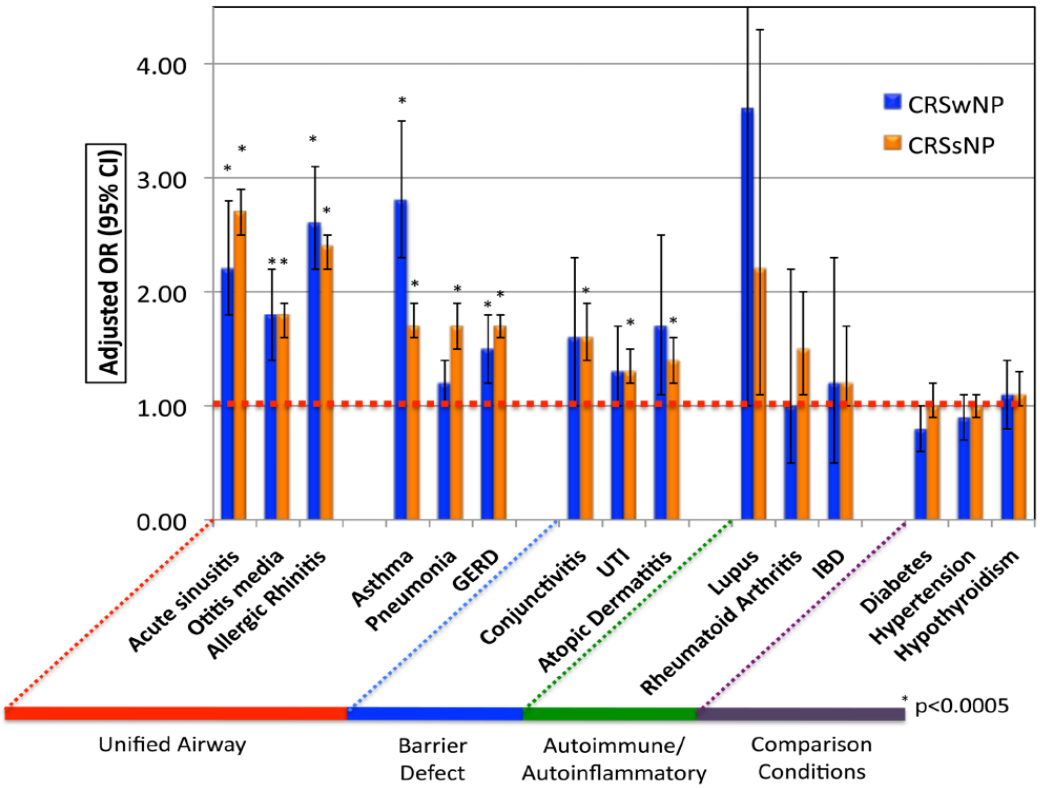

Figure 1.4.1.1.1. Adjusted associations comparing CRSwNP and CRSSNP with control patients (represented by the dotted red line) using selected provider coded diagnoses for the entire observed duration prior to CRS diagnosis. Tan et al. 2013. Incidence and associated pre-morbid diagnoses of patients with chronic rhinosinusitis. *J Allergy Clin Immunol*, 131(5):1350-1360. doi:10.1016/j.jaci.2013.02.002.

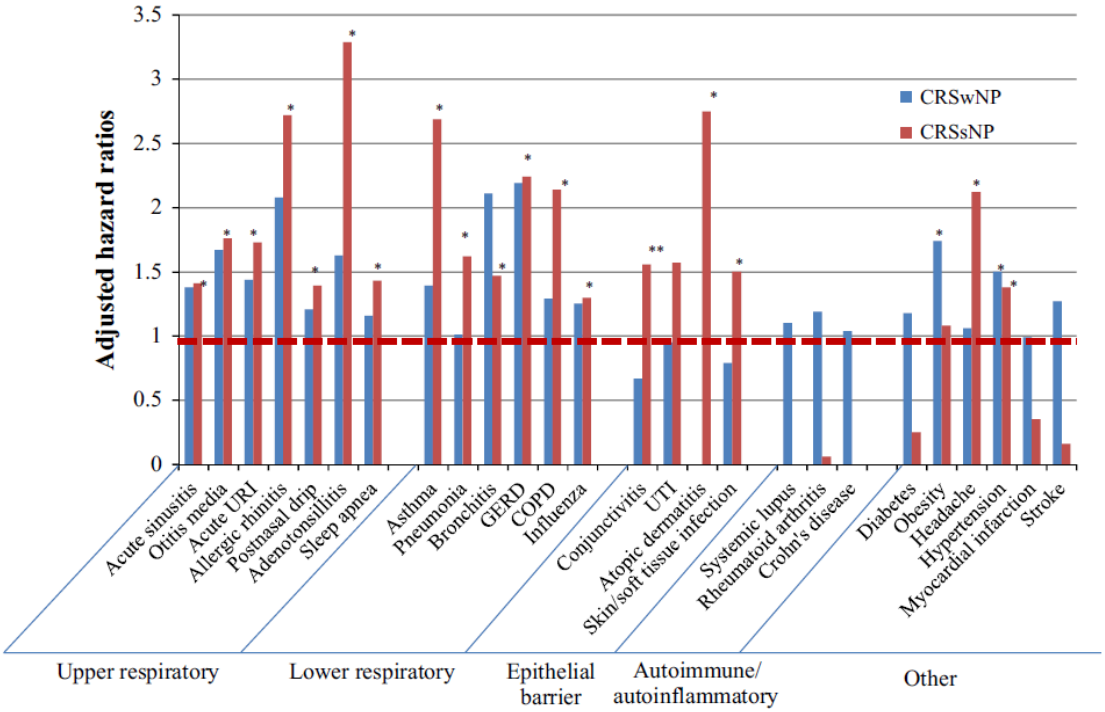

Figure 1.4.1.1.2. Adjusted hazard ratios comparing incident disease among patients with CRSwNP and patients with CRSSNP compared to control patients (dotted red line). GERD, gastrointestinal esophageal reflux disease; UTI, urinary tract infection; COPD, chronic obstructive pulmonary disease. *$P < 0.05$. Hirsch et al. 2015. Five-year risk of incident disease following a diagnosis of chronic rhinosinusitis. *Allergy*, 70:1613-1621.

1.4.2 Pathogenesis of allergic rhinitis

The hallmark of allergic rhinitis, as previously mentioned, is an exaggerated IgE-specific immune response upon exposure to foreign materials, i.e. allergens, classically representing type I hypersensitivity. This process of “sensitization” begins when APCs (e.g., dendritic cells) in nasal mucosa interact with allergens, presenting portions of the allergens (i.e. peptides) on the MHC-II, and forming a ligand to which naïve (undifferentiated) $CD4^+$ T-cells bind and begin differentiation into allergen-specific Th2 cells.[101] Cytokines secreted by Th2 cells induce isotype switching of B cells, the antibody producing cells of the adaptive immune system, to which allergen-specific IgE is produced. Additionally, proliferation of eosinophils, neutrophils, and mast cells occurs in tandem, mounting the atopic response to the allergen.[101]

The priming of mast cells comprises the "early" reaction to an allergen, with symptoms of sneezing, epiphora, and rhinorrhea ensuing due to an influx of histamine, prostaglandin, and leukotrienes. This is followed by the "late" reaction which is marked by expansion of eosinophils, resulting in nasal obstruction as a consequence of nasal tissue damage and remodeling.[101]

1.4.3 Pathogenesis of asthma

The hallmarks of asthma include airway inflammation, airway hyperresponsiveness (AHR), airway remodeling, and bronchoconstriction.[8,102] The classic paradigm of asthma suggested that disease manifested due to a skewed Th2/Th1 polarization of the immune system, with Th2-mediated (type 2) inflammation dominating. However, individuals with a low Th2 profile have been shown to develop asthma, too.[102-105] We limit our discussion of asthma to the major phenotype of Th2-mediated (allergic) asthma.

Among the Th2-dominant individuals, similarly to allergic rhinitis, there is a dominance of allergen-specific IgE as well as eosinophilia.[8,102] These eosinophils move into lung tissue via Th2 cytokine (e.g. IL-4 and IL5) mediation, adherence to vascular endothelia, and migration aided by eotaxin chemokines (e.g., CCL11, CCL24, CCL26).[102] Tissue-implanted eosinophils release several proteins, including those which induce lung damage (eosinophil cationic protein [ECP], eosinophil-derived neurotoxin [EDN], eosinophil peroxidase [EPO], and major basic protein [MBP]),[106,107] airway hyperresponsiveness (MBP),[107] and bronchoconstriction.[106]

1.4.4 Interrelations of biological mechanisms

We limit our discussion of interrelated biological mechanisms for allergic rhinitis, asthma, and CRS to upper and lower respiratory system crosstalk (**Figure 1.4.4.1**).[108]

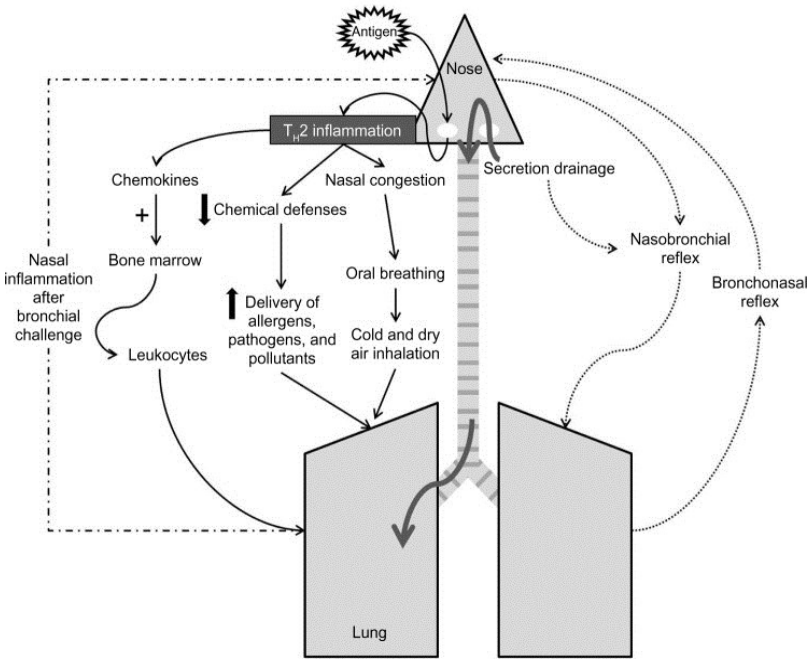

Figure 1.4.4.1. Unified airway disease: pathophysiologic al interaction. Giavina-Bianchi et al. 2016. Unified airway disease: current perspectives. *J Asthma Allergy*, 9:93-100. doi:10.2147/JAA.S81541.

Inflammatory crosstalk, the ability of stimuli in one site to induce inflammation in a distal site, has been previously demonstrated in individuals with asthma and allergic rhinitis.[109] Bronchoscopy-directed antigen placement onto bronchial mucosa induced nasal inflammation within a short period of time. The same inflammatory consequence occurred in pulmonary tissue when antigen was placed on nasal mucosa.[109] This may be expected considering the immune cells and inflammatory mechanisms invoked by allergic rhinitis, asthma, and CRS (especially Th2-mediated CRS) are nearly identical, though acting on different tissues and distal sites of the body. Therefore, localized inflammation may be responsible for pathogenesis of one particular condition; however, diffuse, systemic inflammatory processes may be responsible for sequelae related to development of subsequent morbidities. This concept is supported by improvements in, for example, asthma symptoms following treatment for CRS (among individuals with both conditions).[110,111]

1.5 Risk factors for CRS

In this section, we provide an overview of the risk factors for CRS, identified in previous studies. We first introduce the demographic (e.g., sex, race/ethnicity, age) risk factors followed by lifestyle/social (e.g., smoking status, alcohol use, socioeconomic status [SES]) risk factors, but we primarily focus on sex differences in CRS prevalence and risk. We do not discuss allergic rhinitis or asthma as these have already been covered in sections above. We specify which definition of CRS was used in the study as well as phenotype, if reported.

1.5.1 Demographic and lifestyle risk factors

Sex differences in CRS have been reported with respect to prevalence, reported symptoms, comorbidities, and phenotypes.[112] First considering self-reported physician-diagnosed CRS (CRS_{SR}), large North American surveys have estimated the prevalence of CRS_{SR} to be two-fold greater among females than males.[53,113,114] This sex difference in prevalence, however, was not observed in a comparable survey analysis in Korea.[115] CRS_{ICD} has yielded mixed results regarding sex differences in prevalence. For example, a study of individuals in Pennsylvania showed males were more likely than females to have ICD-9 codes for CRS_SNP and CRSwNP.[74] However, a smaller study in Minnesota estimated 67.7% of ICD-9 codes for CRS were among females.[116] Lastly, a study in Taiwan found no differences in CRS_{ICD} prevalence by sex.[117] A GA^2LEN study in Europe estimated an 8% increase in odds of CRS_S in females than males,[69] whereas a study in Pennsylvania similarly estimated increased odds of CRS_S in females, especially if they reported facial pain or pressure (odds ratio: 1.81; 95% confidence interval: 1.32, 2.49).[70] In a separate GA^2LEN publication, males had nearly twice the odds of CRS_O compared to females.[66] Considering CRS_C, the majority of studies have shown either no sex differences overall,[65] or a greater dominance of males with CRSwNP, compared to females.[118-120]

Few studies of CRS (any definition) have assessed racial/ethnic differences in prevalence or risk. One study observed whites/Caucasians were more likely to have CRS_{SR} than non-whites[70]; however, a different study from the same source population saw no differences in CRS_{ICD} incidence by racial/ethnic groups.[74] A large U.S. national survey observed greater prevalence of CRS_{SR} among American Indians compared to other race groups, while Hispanics were less likely to report CRS than non-Hispanic ethnic groups.[113]

Considering differences in CRS risk or prevalence by age, studies have largely shown a positive relation between increased age and CRS_{SR},[53,69,113,114] CRS_{ICD} (CRSwNP only),[74] CRS_S,[69] and CRS_C[115] (CRSwNP[120-122]). However, one study of CRS_S observed a negative overall association with age (though, peak prevalence was observed between ages 50–59)[70] while a study of CRS_C observed no association with age.[65]

Active tobacco smoking (as opposed to passive or secondhand smoking) has been associated with increased odds of CRS_S[64,69,70,99] as well as CRS_O,[66] but not with CRS_C.[65] Similar to sex differences, associations of SES, education, insurance status, and race/ethnicity have been mixed. A study of CRS_S in Pennsylvania observed a positive association with receipt of Medical Assistance (a proxy for family socioeconomic status),[70] while a study in China observed no association of education level with CRS_S.[64] A prior study of CRS_{SR} similarly observed no association with low income status.[53] Considering CRS_C, studies have shown positive associations with lower education status,[115,122] while others have observed no associations with education[65,123] and socioeconomic status.[115,123]

1.5.2 Environmental and occupational risk factors

Pursuant with the immune-barrier hypothesis, the mucosa of the nose and paranasal sinuses are likely to have the first contact with various exposures (e.g. secondhand smoke, dust, fumes, allergens); therefore, it is believed that environmental and occupational exposures may not only be the driving forces behind disease transition from acute to chronic rhinosinusitis, but for acute exacerbation, too.[124] A recent systematic review found 41 peer-reviewed articles that evaluated environmental and/or occupational exposures in relation to CRS (excluded from the review were studies of secondhand smoke exposure, since this had been reviewed extensively in previous literature, and which did appear to be associated with CRS prevalence, persistence, or response to treatment).[125,126] Of the reviewed studies, the vast majority (40 articles) evaluated occupational exposures, with only one focusing solely on environmental exposures.[127] Only five of the 41 included studies were cohort-studies, four of which were occupational cohorts,[128-131] with the remaining study only focusing on CRSwNP.[132] Only two of the studies used a case definition which was "probable CRS" (a definition which specifically mentioned use of objective evidence of inflammation by CT or nasal endoscopy, i.e. CRS_C).[129,132] Considering all occupational studies with a "probable CRS" case definition, significant exposures included: employment as a deep sea fisherman[133]; dust from cotton textile plant[134]; grain farming[135]; low molecular weight (LMW) compounds[136]; and diving/barotrauma.[129] Of the studies with a "possible CRS" case definition (i.e. CRS_S), significant exposures/occupations included: garage work[137]; plant/machine operators, assemblers, and craft/related trades workers[138]; exposure to gases, fumes, dust or smoke[131,139]; glass-blowing[140]; and pickling and mustard factory work.[141] A recent cross-sectional study in China similarly found occupational exposures to dust, poisonous gas, and carpets to be significant risk factors for CRS_S.[142] Importantly, all of the aforementioned studies used industry, job title, job task, or self-report to

establish exposure metrics, as opposed to primary measurement of toxicants in environmental media.

A study in Norway, using self-reported occupational exposures, observed paper dust, cleaning agents, metal dust, animals, moisture/mold/mildew, and "physically strenuous work" were all associated with CRS_S.[143] A U.S. study using a more formal assessment of exposure to air pollutants (specifically fine particulate matter [$PM_{2.5}$] and black carbon [BC]) via Pittsburgh-area air pollution monitoring stations, observed associations between increased $PM_{2.5}$ exposures and number of functional endoscopic sinus surgeries (FESS) as well as increased BC exposure and increased sinonasal outcome test (SNOT)-22 scores (indicating greater reporting of symptoms), among individuals with clinically diagnosed CRS_SNP.[144]

Additional studies investigating environmental and occupational risk factors for CRS, especially CRS_C, and among individuals selected from a general population sample, are needed to better identify and understand the roles they may play in CRS etiology.

1.6 Cost of illness

Costs of an illness (COI), often referred to as "burden of disease" (BOD), are generally broken into three components: direct, indirect, and intangible costs.[145] While the methodologies employed in COI studies vary considerably from field to field, their primary purpose is to provide quantifiable estimates of the impact illnesses have on society, employers, and individuals.[146] Below, we define and describe the two largest components of COI, direct and indirect costs, followed by these costs as they relate to CRS. We do not discuss intangible costs as there is no consensus about what constitutes these costs.[145]

Direct costs are those which are immediately related to the diagnosis, management, or treatment of a condition. For example, clinician office visits, diagnostic testing, use of

medical products, health care services, and medications are all direct costs of illness.[145,146] Indirect costs are those which relate to impacts of the condition on daily functioning and livelihood. For example, missing work due to illness (i.e. absenteeism) and reduced productivity while at work due to illness (i.e. presenteeism) are the biggest contributors to indirect costs of illness.[146-148] While it may be intuitive for direct costs of illness to be greater than indirect costs, the converse is generally true, with indirect costs amounting to an average of 2.3-times more than direct costs.[148]

1.6.1 Workplace impacts of CRS

A recent systematic review focused on characterizing the economic impact of adult CRS in the United States.[149] Of the 44 papers selected for inclusion, four studies assessed the direct costs of CRS[150-153] while only two assessed the indirect costs.[154,155] Considering direct medical costs only, the most commonly referenced estimate suggested adult CRS_{ICD} incurred an incremental cost of $8.6 billion,[152] which approximates $9.9 billion in 2014, accounting for inflation.[149] However, a study published in 2015—using the same data source as well as regression models and selection weights, estimated the national incremental cost (additive costs due to illness; derived by subtracting costs in those with illness from those in otherwise comparable individuals without illness) of CRS_{ICD} to be $12.5 billion per year.[156] Authors assumed a national prevalence of CRS to be 3.5%, estimating the total national expense of the condition to be $60.6 billion, annually.[156]

Indirect costs of CRS have received much less attention, compared to the direct costs. A previous study used a prospective cohort of CRS_C patients to assess indirect costs by measuring workplace lost productivity time (LPT), an overall estimate of workplace impacts combining absenteeism and presenteeism,[157] finding annual costs of $619 per patient in 1999,[154] which would be $884 per patient in 2014.[149] The most recent

study to estimate indirect costs of CRS, though restricted to refractory (recalcitrant) CRS_C cases, used a small prospective cohort and estimated a cost of $10,077 per patient per year—$12.8 billion overall—using lost productivity costs.[155]

Importantly, no prior studies of the workplace impacts of CRS have been completed using individuals selected from the general population, which was an aim of this dissertation. Further, no prior studies have included individuals across the broad spectrum of sinus disease (most have been of individuals from tertiary referral clinics), nor have they accounted for comorbidities with overlapping symptomatology (e.g., allergic rhinitis, asthma, migraine headache).

1.7 Clinical diagnoses

While we did not study healthcare economics, resource utilization, or disparities in healthcare access and referral in this dissertation, it was important to understand the general process by which an individual receives a clinical diagnosis of a condition, as we used self-reported physician diagnosed comorbidities in our analyses. Therefore, in this section, we introduce a broad framework to understand how an individual receives a clinical diagnosis, followed by a framework specific to the diagnosis of CRS. We extend the latter by discussing the role of subjective measures in relation to CRS and associated conditions; and the role of objective measures (i.e., endoscopy, MRI, and CT imaging) in the diagnosis and study of CRS.

1.7.1 Framework for clinical diagnosis

The Committee on Diagnostic Error in Health Care of the National Academies of Sciences, Engineering, and Medicine developed a framework to better understand the process of clinical diagnosis, with the broader lens of improving diagnosis through reduction in diagnostic errors.[158] The process of diagnosis is inherently patient-centered, meaning the needs and wants of the patient are equally important to those of the

clinician, stresses that patient education and self-advocacy are critical,[158,159] and is highly iterative (**Figure 1.7.1.1**).[158]

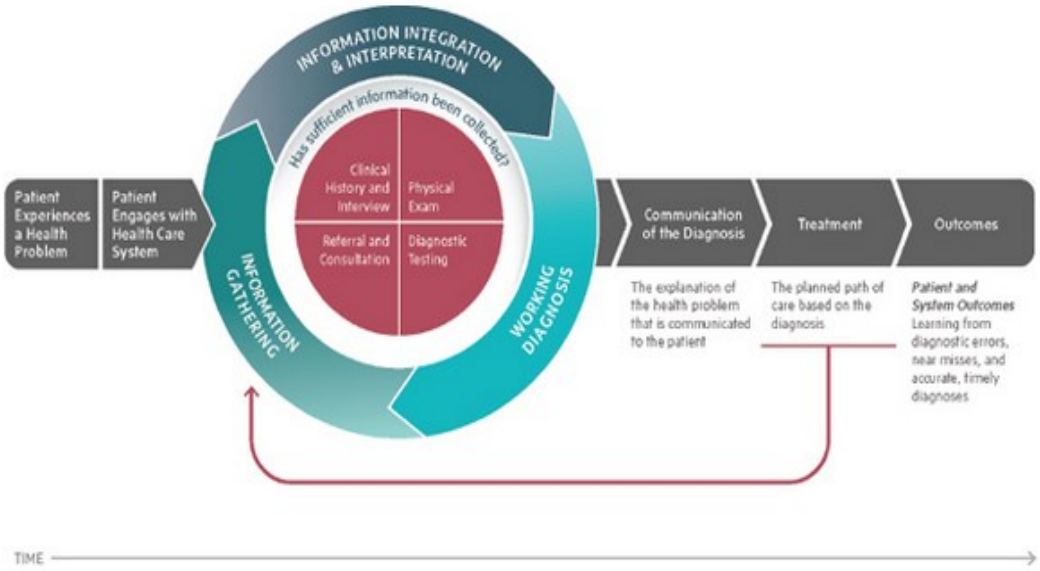

Figure 1.7.1.1. Framework of clinical diagnosis proposed by the Committee on Diagnostic Error in Health Care of the National Academies of Sciences, Engineering, and Medicine. Ball J, Balogh E, Miller BT. Improving diagnosis in health care: National Academies Press 2015.

As represented by the framework, the first step in receiving a diagnosis is an individual experiencing symptoms. The second step occurs if and when the individual seeks medical care for their symptoms. While the committee did not include the factors related to whether an individual seeks medical care for symptoms in their framework or explanation, there are additional considerations between the first two steps: 1) Is this the first time these symptoms have been experienced? 2) Are they (subjectively) severe enough to prompt seeking of medical care? 3) Are there barriers to receiving medical care even if the need for it is presented? The next step is actually a series of iterative and co-dependent steps wherein information is gathered, integrated, and interpreted to culminate in a working diagnosis or several working diagnoses. Information gathered includes clinical history and interview, physical exam, objective diagnostic testing, and perhaps referral or consultation with other clinicians/specialists. As diagnoses are ruled

out by subjective and objective measures, the remaining working diagnoses are comparatively verified against the individual's contextual influences (e.g., physiology, demographics, comorbidities, other risk factors) until a (tentatively) final diagnosis is made. At that point, the clinician communicates to the individual the diagnosis, its implications, course of treatment, and next steps. Treatment is then initiated with follow-up being critical to determine if the initial diagnosis was accurate and whether positive outcomes are observed for the individual.[158]

1.7.2 Clinical diagnosis of CRS

As previously mentioned, several consensus groups have advised a clinical definition of CRS (i.e. CRS_C) to not only include a certain combination of reported symptoms, but confirmation of inflammation via objective measures, too.[1-3] While it has been argued that symptom-based definitions of CRS (i.e. CRS_S) are useful because symptoms are what drive individuals to seek care (and thus, receive a diagnosis), objective evidence is necessary to provide differential diagnosis and targeted treatment for symptoms.[1]

In general, individuals transition from being asymptomatic to experiencing NSS.[17] Individuals with NSS, depending on the duration, severity, or bother of symptoms may first use over-the-counter products, and then, if there isn't sufficient relief, seek medical care whereby presumptive treatment (active measures at treating symptoms without formal diagnosis) could include antibiotics, oral (systemic) or inhaled corticosteroids, antihistamines, and nasal irrigation or nasal saline spray.[1,10] These symptoms may resolve, be recurrent, or persist with duration and frequency of symptoms narrowing possible diagnoses.[1-3,10] Whereas infrequent or readily remitted symptoms may be an indication of ARS or allergic rhinitis,[1,160] persistent symptoms over required periods of time (i.e. 12 weeks) may indicate CRS.[1-3,10] Considering individuals with "true CRS" (not formally diagnosed but have the underlying pathology), they may iteratively seek care,

be presumptively treated, remit, develop symptoms, and start the process again.[17] After several rounds of long-term unsuccessful treatment, they may receive further diagnostic testing to begin ruling in/out possible diagnoses, with endoscopy, MRI, or CT used for confirmation of CRS_C as diagnosed by an otorhinolaryngologist or the primary care physician.[1-3,10] However, these objective measures are usually only performed on individuals where surgical intervention is likely to be initiated, representing a small percentage of individuals on the spectrum of sinus disease. Below, we present a series of flow-diagrams highlighting the clinical process by which diagnosis of ARS (**Figures 1.7.2.1** and **1.7.2.2**) or CRS (**Figures 1.7.2.3–1.7.2.5**) occurs. Although this consideration is not directly relevant to the research presented herein, it is helpful to understand the clinical decision-making process and how it may influence the range of conditions that have been labeled as "CRS" in the literature.

Diagnosis of ARS in the primary-care setting is common and generally uncomplicated[1]; however, severe or recalcitrant ARS (e.g. ABRS) is often referred to an otorhinolaryngologist (**Figure 1.7.2.1**).[1,10] In a specialist-care setting, severe ARS often results in directed medical therapies, including culture-based antibiotics (if bacterial presence confirmed) and oral steroids, as well as endoscopy, MRI, or CT imaging for ruling-in surgical intervention (**Figure 1.7.2.2**).[1,10]

The diagnostic process for CRS in a primary-care setting is similar to that of ARS, albeit with different definitional operationalization, though referral to an ENT is recommended more often in CRS than ARS (**Figure 1.7.2.3**).[1] In a specialist-care setting, phenotyping of CRS is usually performed via nasal endoscopy (to confirm presence of nasal polyps), with subsequent medical and surgical therapies tailored to the observed phenotype (CRSwNP or CRS_SNP). While both phenotypes often receive the same medical treatment (e.g., oral steroids, nasal inhaled steroids, antibiotics),

surgical interventions are more readily performed in those with nasal polyps (**Figure 1.7.2.4**), compared to those without (**Figure 1.7.2.5**).[161]

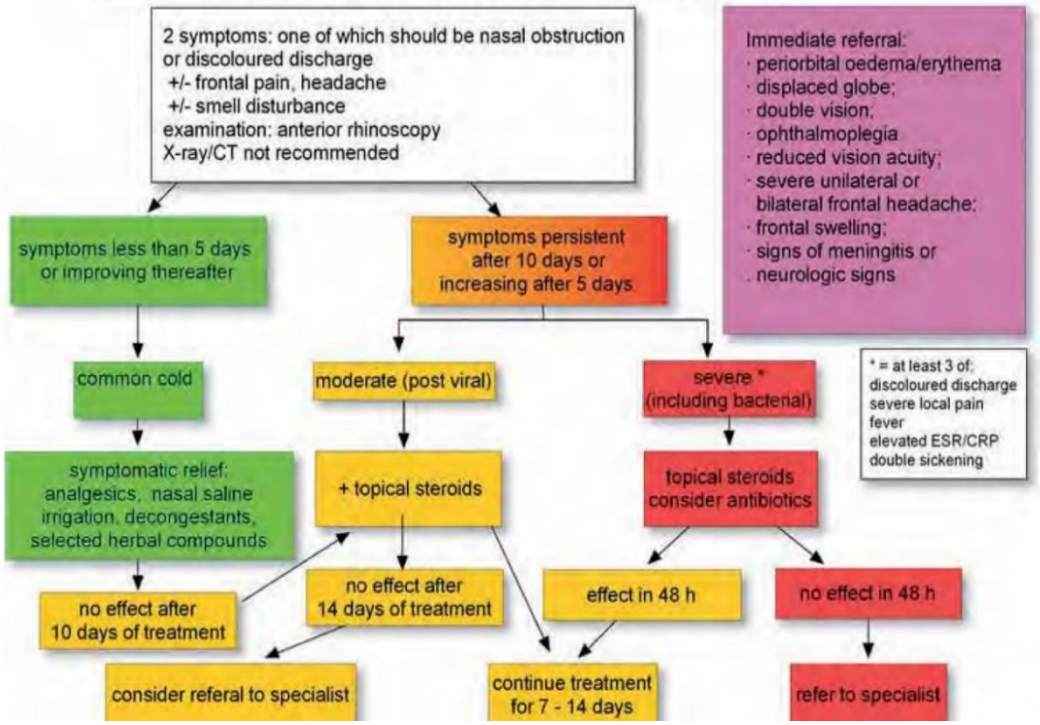

Figure 1.7.2.1. Flow diagram of ARS clinical diagnosis and recommended treatments and courses of action, in a primary-care setting. Adapted from Fokkens WJ, Lund VJ, Mullol J, et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2012. *Rhinol Suppl* 2012(23):3 p preceding table of contents, 1-298. [published Online First: 2012/07/07]

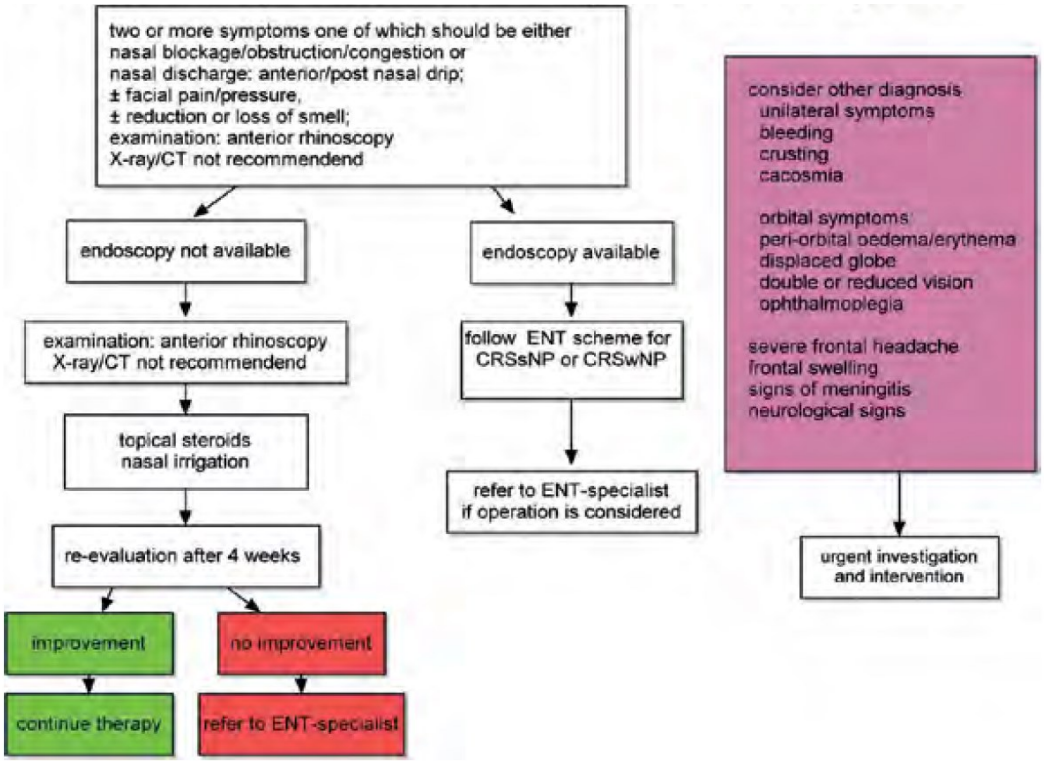

Figure 1.7.2.2. Flow diagram of ARS clinical diagnosis and recommended treatments and courses of action, in a specialist-care setting. Adapted from Fokkens WJ, Lund VJ, Mullol J, et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2012. *Rhinol Suppl* 2012(23):3 preceding table of contents, 1-298. [published Online First: 2012/07/07

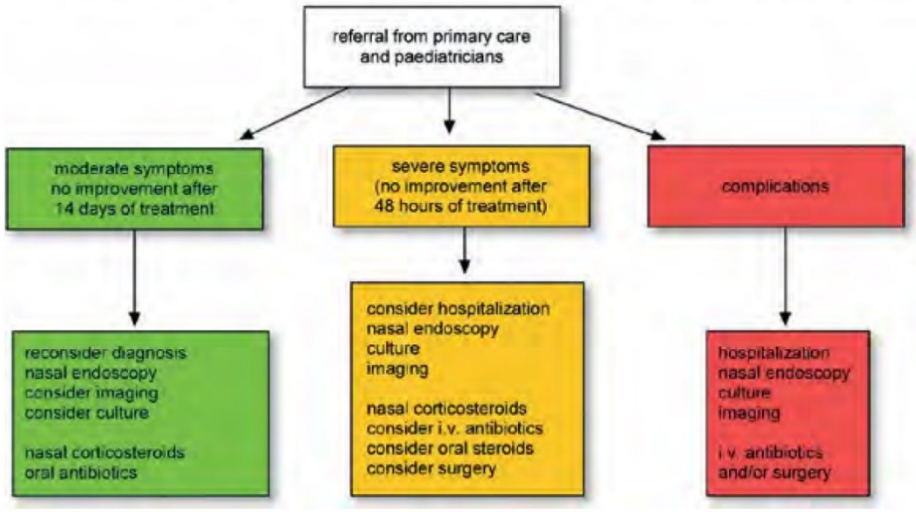

Figure 1.7.2.3. Flow diagram of CRS clinical diagnosis and recommended treatments and courses of action, in a primary-care setting. Adapted from Fokkens WJ, Lund VJ, Mullol J, et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2012. *Rhinol Suppl* 2012(23):3 p preceding table of contents, 1-298. [published Online First: 2012/07/07

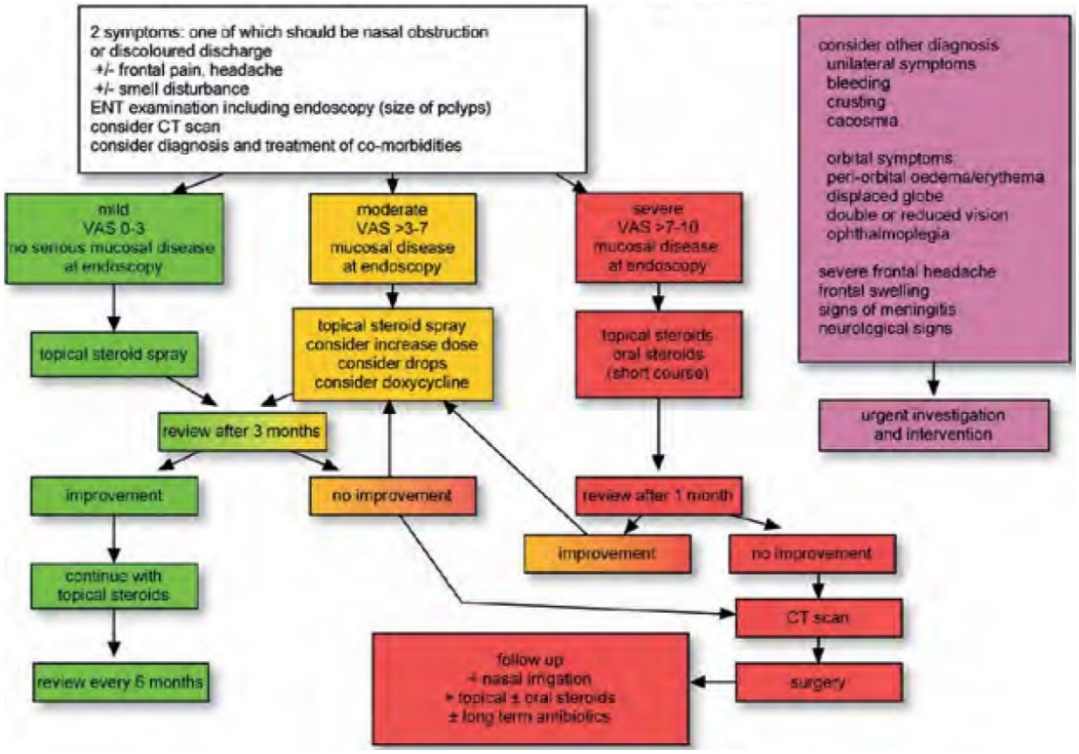

Figure 1.7.2.4. Flow diagram of CRSwNP clinical diagnosis and recommended treatments and courses of action, in a specialist-care setting. Adapted from Fokkens WJ, Lund VJ, Mullol J, et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2012. *Rhinol Suppl* 2012(23):3 p preceding table of contents, 1-298. [published Online First: 2012/07/07]

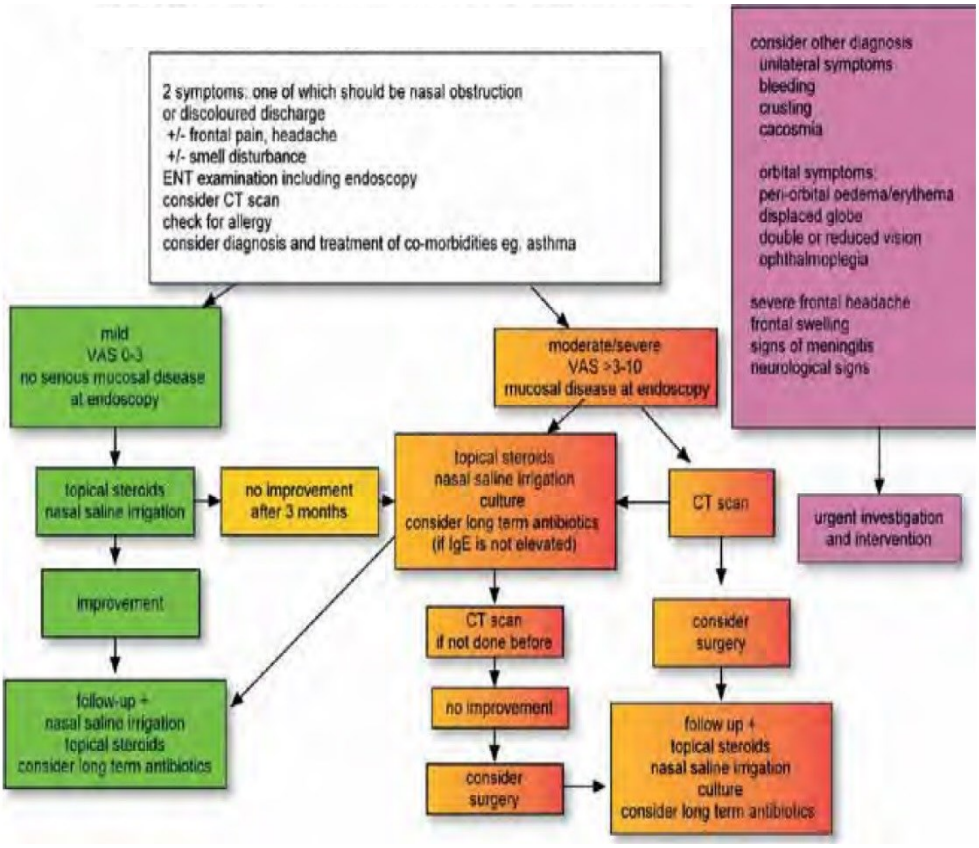

Figure 1.7.2.5 Flow diagram of CRSsNP clinical diagnosis and recommended treatments and courses of action, in a specialist-care setting. Adapted from Fokkens WJ, Lund VJ, Mullol J, et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2012. *Rhinol Suppl* 2012(23):3 p preceding table of contents, 1-298. [published Online First: 2012/07/07]

1.7.3 Subjective measures of disease

Following the argument in the previous section, symptoms are the manifestation of underlying pathology, which are usually the reason why an individual seeks medical care.[158] Some conditions have diagnostic criteria based solely on symptoms. For example, migraine headache is primarily based on the reporting of three specific symptoms during headache episodes: nausea, photophobia (sensitivity to light), and disability (inability to function productively, as usual).[162] Similarly, viral colds (i.e. ARS) are diagnosed based on duration and frequency of specific symptoms.[1] While clinical diagnosis of allergic rhinitis,[160] asthma,[163] and CRS[1-3] is usually done based on presentation of signs and symptoms alone, consensus guidelines recommend using

objective measures in order to guide therapies and prognostication. Below, we outline the symptom-based components of these overlapping conditions.

1.7.3.1 *Allergic rhinitis*

Allergic rhinitis is often diagnosed by the presence of two or more symptoms, with near daily frequency and duration of at least one hour, including nasal congestion, nasal itching, sneezing, and rhinorrhea.[160]

1.7.3.2 *Asthma*

Asthma is often diagnosed by history of wheeze, shortness of breath, chest tightness, and cough. These symptoms should vary in intensity and severity over time (i.e. should not be persistent).[163]

1.7.3.3 *Chronic rhinosinusitis*

As previously described, CRS is characterized by symptoms of nasal blockage/congestion, nasal discharge (anterior and/or posterior), smell loss, and facial pain/pressure. These symptoms must have a duration of at least 12 weeks.[1]

1.7.4 Utility of symptoms in diagnosis and study of CRS

Symptoms are critically important not only in the accurate diagnosis of CRS,[1] but in the study of CRS, too. As shown in previous sections, symptoms are the driving force behind an individual seeking medical care in the first place. Further, individuals generally care most about the treatment and abatement of their symptoms, as opposed to underlying pathogenesis or pathophysiology. This highlights an important dichotomy in medical care, one which was highlighted in the aforementioned discussion of patient-centered care[158,159]: patients care about symptoms, physicians care about underlying processes resulting in those symptoms that can direct care. This dichotomy is manifested in research settings, too. Studies of CRS_S are important in that they can provide deeper understanding of the risk factors for—and implications of—symptoms.[69,70,164] However, symptom-based definitions like CRS_S are limited in their ability to connect to biological mechanisms underpinning the manifestation of said

symptoms, without careful consideration for overlapping symptomatology with other morbidities. In essence, epidemiologic studies of CRS_S are likely more prone to misclassification of disease than CRS_O or CRS_C, given the commonality of qualifying CRS_S symptoms with other (often) comorbid conditions, thus biasing observed associations. Therefore, studies of CRS_S are perhaps best at exploration and hypothesis generation, as opposed to causal inference.

1.7.5 Objective measures of inflammation and disease

Objective measures of inflammation and/or disease help to narrow potential diagnoses, guide medical and surgical therapies as well as prognostication, and establish potential etiologic sources of disease onset. In that sense, objective measures can compensate for the measurement error induced by high-sensitivity/low-specificity subjective measures (i.e. symptoms), assuming they both measure the same underlying phenomenon (e.g. CRS).[165]

Several conditions include objective measures as part of a clinical diagnosis. Asthma diagnosis, for example, requires evidence of airway obstruction and demonstration of variability in degree of obstruction, both usually measured by spirometry.[163] CRS, as aforementioned, requires confirmation of sinus inflammation and/or nasal polyps via endoscopy, MRI, or CT.[1-3]

1.7.6 Utility of endoscopy, MRI, and CT in diagnosis and study of CRS

While we only utilized sinus CT scans in this dissertation, we discuss the other common modes of objective confirmation of inflammation in the presence of NSS in diagnosis of CRS, identifying advantages and disadvantages of each.

1.7.6.1 *Endoscopy*

While the endoscope has been around since the 1950's, nasal endoscopic findings were not considered as part of the diagnostic criteria for CRS until 2007, with the AAO-HNS including it as sufficient objective evidence (next to the gold standard, sinus CT).[166] Nasal endoscopy, while not the gold standard because of high specificity but low sensitivity, does allow the direct visualization of the nasal cavity and nasopharynx, and is often used to confirm the presence of nasal polyps (which usually grow outward from the ethmoids down into the nasal cavity). **Figure 1.7.6.1.1** shows an obstructive nasal polyp identified by nasal endoscopy.[167] Several studies have shown the inter-rater agreement for polyps, purulence, or anatomical abnormalities to be high[168-170]; however, mucosal changes (e.g., edema and thickening) and middle turbinate obstruction require other forms of imaging (i.e., MRI or CT).[168,170]

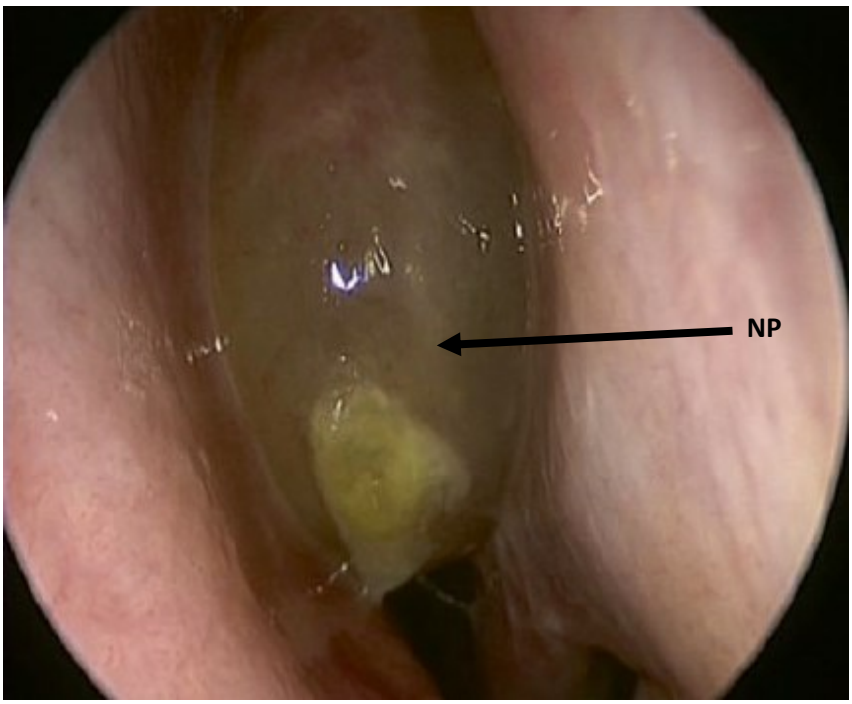

Figure 1.7.6.1.1. Nasal endoscopic visualization of obstructive nasal polyp (NP). Wiedermann J, Bury SB, Singh A. Endoscopic Diagnosis of Chronic Rhinosinusitis. In: Batra PS, Han JK, eds. Practical Medical and Surgical Management of Chronic Rhinosinusitis. Cham: Springer International Publishing 2015:29-41.

1.7.6.2 *Magnetic resonance imaging*

While not often used in diagnosis of CRS, at least as a first-pass imaging choice, MRI is used in suspected (or confirmed) cases of CRS where there is recalcitrant sinus

infection with ocular and/or intracranial complications, or development lesions.[10,171] Contributing to the low use of MRI in cases of CRS are high cost, longer imaging time, and lack of bone detail.[172-174] **Figure 1.7.6.2.1** compares axial images of the paranasal sinuses obtained by CT (**Figure 1.7.6.2.1a**) and MRI (**Figure 1.7.6.2.1b**).[171] The images demonstrate that the level of soft tissue characterization achieved by MRI is

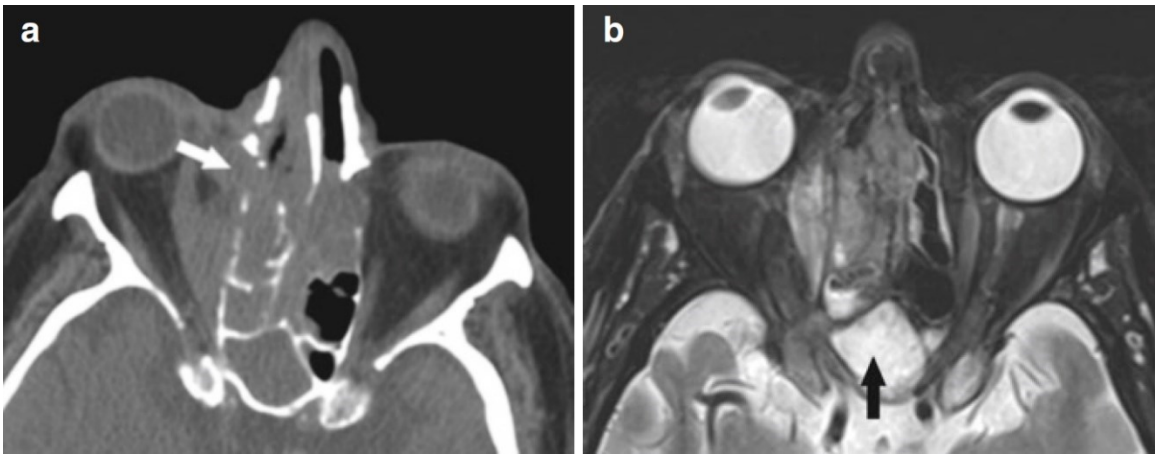

Figure 1.7.6.2.1. Comparison of sinus CT and sinus MRI. (a) Axial CT images showing a polypoid soft tissue mass centered in the right sinonasal cavity, crossing midline to the left, with extrasinus extension into the right orbit and destructive non-expansile bony changes (*arrow*). This is concerning for an aggressive process (malignancy or aggressive infection in the appropriate clinical scenario). MRI should be obtained. (b) Axial T2w MR images showing an infi ltrative mass centered in the right ethmoid air cells, extending into the right orbit, relatively T2 hypointense compared to the benign post-obstructive sinonasal secretions in the sphenoid sinus (*black arrow*). Flanagan CE, Baugnon KL, DelGaudio JM. Radiographic Diagnosis of Chronic Rhinosinusitis. In: Batra PS, Han JK, eds. Practical Medical and Surgical Management of Chronic Rhinosinusitis. Cham: Springer International Publishing 2015:43-72.

unparalleled; however, bony mass and structures are more clearly identified on CT.

1.7.6.3 *Computed tomography*

As previously mentioned, sinus CT is the gold standard in imaging for suspected CRS because of its speed and resolution of bony structures and mucosal thickening.[10,171] In brief, a CT leverages variability in X-ray absorption by tissues of differing densities, taking several cross-sectional images during the process.[1] Sinus inflammation appears on CT as opaque regions in normally void sinuses, which appear black on CT (**Figure 1.7.6.3.1**).[171] In addition to mucosal thickening (i.e. submucosal

edema), partial or complete opacification, and nasal polyps, changes to bony regions of the sinuses (e.g., thickened, sclerotic, and hyperostotic bone) can also be observed on CT (**Figure 1.7.6.3.2**).[10,171]

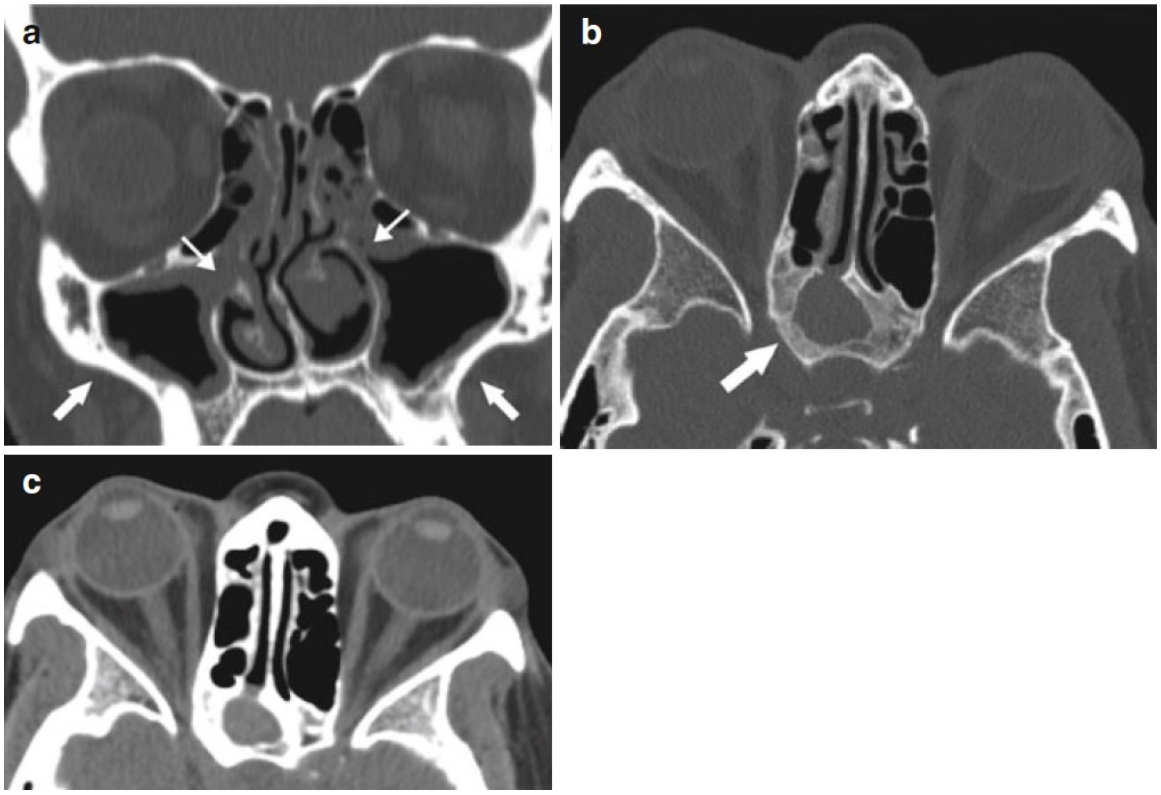

Figure 1.7.6.3.1. Varied appearance of chronic rhinosinusitis. (**a**) Coronal image showing bilateral maxillary sinus mucosal thickening, extending into the outflow tracts (*thin arrows*). Note the sclerosis and thickening of the surrounding maxillary sinus walls (*thick arrow*). Axial images in bone window (**b**) and soft tissue window (**c**), demonstrating chronic right sphenoid sinusitis, recurrent postoperatively, with opacification with high-density secretions extending through the sphenoid ostium and sclerosis and hyperostosis of the surrounding bone (*thick arrow*). Flanagan CE, Baugnon KL, DelGaudio JM. Radiographic Diagnosis of Chronic Rhinosinusitis. In: Batra PS, Han JK, eds. Practical Medical and Surgical Management of Chronic Rhinosinusitis. Cham: Springer International Publishing 2015:43-72.

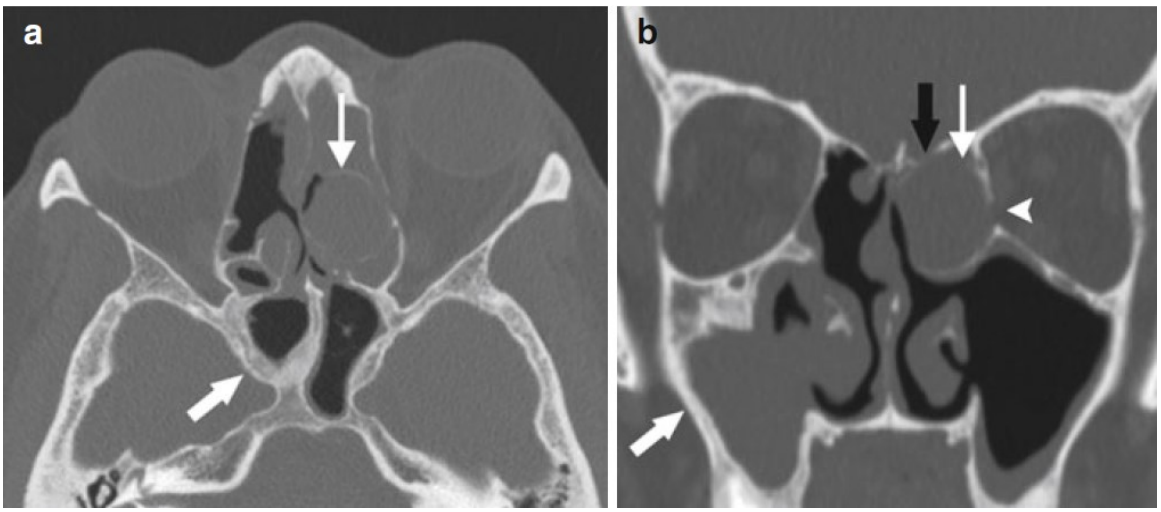

Figure 1.7.6.3.2. Bony changes with chronic sinusitis. Axial (a) and coronal (b) images of a patient with recurrent chronic sinusitis after endoscopic sinus surgery, with thickening and sclerosis surrounding chronic sinusitis within the sphenoid and the right greater than the left maxillary sinuses (*thick arrows*), as well as bony remodeling and expansion surrounding an opacified left ethmoid air cell, compatible with mucocele (*thin arrow*). Note the thinning and dehiscence of the left lateral lamella (*black arrow*) and the left lamina papyracea (*arrowhead)* from the expansion of the mucocele. Flanagan CE, Baugnon KL, DelGaudio JM. Radiographic Diagnosis of Chronic Rhinosinusitis. In: Batra PS, Han JK, eds. Practical Medical and Surgical Management of Chronic Rhinosinusitis. Cham: Springer International Publishing 2015:43-72.

1.8 Limitations of current measurement practices

1.8.1 Construct validity of CRS_S

There are several possible sources of error in CRS_S operationalization. For example, four symptom groups comprise CRS_S (nasal blockage/congestion; nasal discharge [anterior or posterior]; smell loss; and facial pain/pressure), yet two of the symptom groups (nasal discharge and facial pain/pressure) pertain to multiple symptoms with possibly disparate etiologic and pathogenic origins. By assuming exchangeability of anterior nasal discharge for posterior, and facial pain for facial pressure, one assumes that these symptoms manifest from the same underlying biological process, which may or may not be true. Further, while nasal blockage/congestion and nasal discharge are anchoring symptoms (at least one is required for CRS_S), secondary symptoms of smell loss and facial pain/pressure are also essentially exchangeable with one another (i.e. two people with nasal blockage—one with smell loss the other with facial pain—would

both be considered to have CRS_S). Considering the evidence towards endotypes of CRS, as opposed to broad phenotypes, treating these symptoms as exchangeable may mask connections to relevant endotypes.[175] For example, a prior study of tertiary care subjects receiving a sinus CT scan for CRS symptoms found substantial overlap between CRS and non-CRS groups, noting facial pain to be negatively predictive of CRS while smell loss was positively predictive.[176] This is perhaps unsurprising given the nonspecific nature of facial pain, which is commonly reported in several conditions. For example, facial pain is often reported in migraine headache and orodental diseases.[1]

Only one study has assessed whether CRS_S operationalization is consistent with the idea that these symptoms measure one underlying construct.[175] Using exploratory factor analysis (EFA), authors tested whether multiple dimensions (i.e. underlying constructs) were measured by a set of 37 NSS, allergy, asthma, and constitutional symptoms (e.g., fatigue, fever, headache), in a general population sample.[175] As many as three CRS-relevant constructs, including nasal blockage/congestion, smell loss, and facial pain/pressure, were identified, further evidence of the weak rationale of current approaches to measurement of CRS_S.

1.8.2 Scoring radiologic inflammation

Radiologic inflammation obtained by CT is most commonly scored using the Lund-Mackay (LM) scoring approach.[177] With this method, opacification is quantified in five sinuses (maxillary, anterior ethmoid, posterior ethmoid, frontal, and sphenoid) by assigning a score of 0 for no opacification, 1 for partial opacification, and 2 for complete opacification, separately for each side (left and right). The OMC is scored as a 0 for less than complete opacification and 2 for complete opacification. These individual sinus scores are then summed to form a total score ranging from 0 to 24, with higher scores indicating greater opacification, and thus greater sinus inflammation.[177] The LM scoring

approach has received criticism for its generally poor ability for tracking disease progression and prognostication, with respect to CRS.[178] As such, the modified Lund-Mackay (mLM) scoring approach was developed.[179] This approach expanded partial opacification (as measured by LM) into thirds, allowing sinus location to have a score ranging from 0 to 4, and a total score of 0 to 44. Despite its greater detail, it has not been shown to perform differently than LM.[179] Importantly, these scoring approaches have not been comparatively assessed in a general population sample, one aim of the research presented herein.

Considering LM, there is no clear indication for which score (or range of scores) constitutes a "positive" CT finding for CRS. However, a previous study of tertiary care patients, receiving sinus CT scans for indications other than CRS, had a mean LM score of 4.26 (95% confidence interval: 3.55, 4.97).[180] The authors concluded that a LM cutoff of 4 (LM < 4) should be used to indicate "normal" sinus opacification. While this cutoff has been used in epidemiologic studies of CRS,[66,181] the sample from which it was based was highly selected and does not likely represent the general population; therefore, this cutoff needs to be reassessed in a more representative sample, another aim of the research in this dissertation.

Additionally, there are several issues with the assumptions implicated by using a single score approach to quantifying or categorizing radiologic inflammation, i.e. LM or mLM. Most importantly, LM and mLM assume all sinus locations are of equal importance and therefore measure the same underlying construct (i.e. CRS). However, it is known that sinus opacification tends to follow known drainage routes (e.g., osteomeatal unit [OMU], sphenoethmoidal recess [SER]).[182] As such, quantification of sinus opacification should likely take into consideration the location of opacification, not just severity. To date, no prior studies of sinus radiologic inflammation have taken into consideration the

location and patterns of opacification, in a general population sample representing a broad spectrum of sinus disease, another aim of this dissertation research.

1.9 Specific aims

As previously described, despite being a particularly burdensome condition,[1-3,70,155,156] previous studies of CRS have differed widely on the definition used to characterize CRS (e.g., CRS_S, CRS_{SR}, CRS_C), making inferences about the condition difficult to assess across studies. Additionally, the majority of CRS epidemiologic studies have focused on individuals selected from tertiary care settings (e.g. surgical clinics), which only represent a small subset of the underlying spectrum of disease. Therefore, studies of individuals from the general population, representing the full spectrum of disease, are necessary.

Like CRS, acute exacerbations of nasal and sinus symptoms (AENSS) related to CRS (i.e. AECRS) have lacked a unifying and consistent definition in prior studies. Of studies focused on AENSS among CRS subjects, most primarily focused on bacteriology and immunology—rather than risk factors—of exacerbation.[20,183-186] As such, comparatively assessing several definitions of AENSS, estimating their prevalence, and identifying their risk factors is of critical importance.[3]

Considering tangible impacts, no studies have assessed the workplace impacts (i.e. absenteeism, presenteeism, and lost productive time) of NSS across a full spectrum of sinus disease (including CRS), among individuals from a general population sample. Identifying which symptoms impart the greatest burden on workplace productivity may help educate clinicians and patients about the consequences of these symptoms and possibly guide further treatment and/or symptom management.

Lastly, the quantification of radiologic inflammation in CRS warrants further investigation. A simple sum of LM opacification scores for six sinus locations is often used to guide a “positive” CT finding indicative of CRS, with a current recommended cutoff of ≥ 4 for the total score.[180] However, this scoring approach assumes all sinus

locations to be interchangeable, which goes against the newer thinking of CRS being represented by several endotypes culminating in few observable phenotypes.[7,12,187] Therefore, newer approaches to characterizing and measuring sinus inflammation are needed.

Data from an existing population-based study[70] was used to understand NSS in the general population. The studies that comprised this dissertation research utilized information from the electronic health record (EHR) of Geisinger, a large healthcare system whose patients are generalizable to the region EHR, longitudinal questionnaire data from 7847 individuals (selected from the EHR), and research sinus CT scans from 646 subjects in the questionnaire study, to holistically understand this condition. The following specific aims were used to address the critical knowledge gaps outlined above:

1. Comparatively assess several definitions of AENSS, estimate their prevalence, and identify risk factors for exacerbation.
2. Estimate the workplace impacts of NSS related to CRS and related conditions.
3. Rigorously assess and improve current approaches to measurement of radiologic inflammation in CRS.

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Chapter 2: Detailed methods

In this chapter, we provide greater background and information about two broad classes of methods used in **Chapters 4 and 5**, specifically regarding exploratory factor analysis (EFA) and latent class analysis (LCA). We include this information to better provide context for why and how these methods were used. However, the following descriptions of these methods are not intended to be fully comprehensive, but rather a brief overview of salient issues relevant to the utility, methodologic decisions, and appropriateness of their use for our applications.

2.0 Chapter 4 and Chapter 5: Factor analysis

2.0.1 Concept and utility

Unlike principal components analysis (PCA), which is often used in the creation of indices (i.e. composite measures formed by several observed indicators), factor analysis is commonly used in scale development, whereby observed indicators are manifestations of unobservable latent constructs. PCA seeks to create uncorrelated (i.e. orthogonal) and weighted combinations (composites) of observed indicators to maximize variance explained by these composites while factor analysis maximizes the common variance of the observed indicators.[1] While two "flavors" of factor analysis are common in practice, confirmatory and exploratory, we restrict our discussions in this section to the latter. EFA is a method in which unobserved (i.e. latent variables that cannot be directly measured) variables are linearly related to manifest (i.e. observed) variables, with no hypothesized relations of the observed and manifest variables *a priori* (unlike confirmatory factor analysis which tests predetermined relations of observed indicators with latent constructs).[1] A common goal of EFA is to reduce dimensionality in observed data, which is done by using covariances among the observed variables to express them in terms of fewer latent variables (i.e. factors), thereby identifying relations of observed indicators with these factors.[2] The general form of the EFA model can be viewed as a

series of linear regression-like models, with independent errors and conditional independence of observed variables (i.e. conditional on the factor, observed variables are independent of each other) (**Equation 2.0.1.1**). The observed variable indicators (Y_k) are linearly related to factor loadings (λ_k), the latent factor (F), and random error (δ_k). The factor loadings are generally interpreted as the correlation of the factor with the observed indicator, though this interpretation is dependent on the rotation method used, with larger absolute values indicating a greater association with the factor.[3] As an example of EFA "in action," we used EFA in **Chapter 5** to determine whether radiologic inflammation in six sinonasal locations were associated with a single underlying factor (i.e. construct), or if there were additional constructs represented by these locations (**Figure 2.0.1.1**). This analysis was directly relevant to the Lund-Mackay approach of treating all sinonasal locations equivalently in summing them to make a single index.

Equation 2.0.1.1. Formulation of EFA as regression-like model

$$Y_1 = \lambda_1 F + \delta_1$$
$$\cdots$$
$$Y_k = \lambda_k F + \delta_k$$

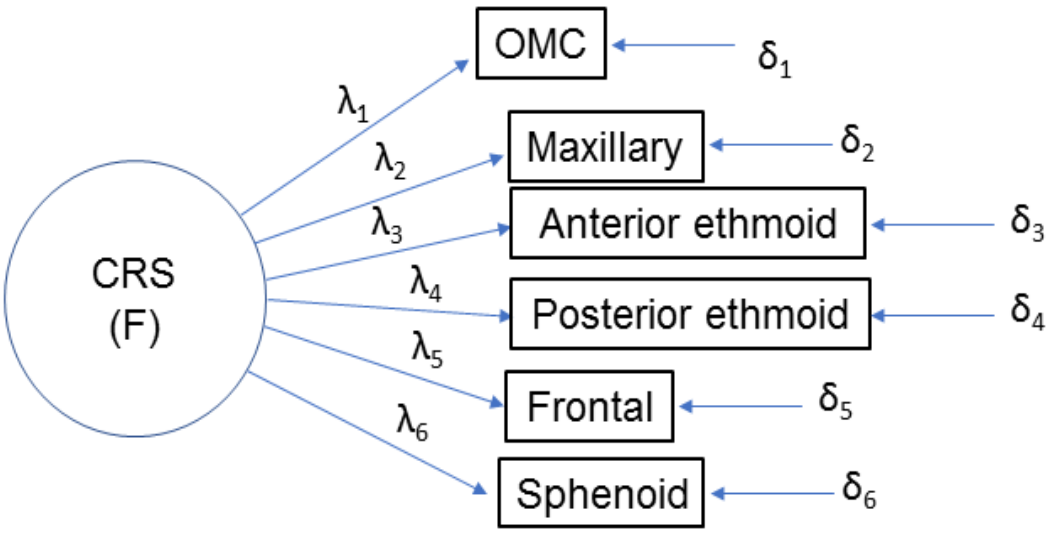

Figure 2.0.1.1. Visual representation of EFA used in Chapter 4

2.0.2 Estimation procedures

2.0.2.1 *Pearson, tetrachoric, polychoric, biserial, and polyserial correlations*

Correlation matrices based on the observed variables are often used as inputs for EFA, as they are essentially standardized covariances, and therefore unitless and bounded by -1 and 1. Pearson correlations are found between sets of continuous observed variables, whereas *inferred* Pearson correlations are found for dichotomous and ordinal variables. Polychoric correlations were used in **Chapters 4** and **5** as the sinus location indicator variables were observed to be ordinal. In brief, polychoric correlations are considered inferred Pearson correlations because the estimated correlation is that of two underlying (i.e. latent) normal random variables, which manifest as the observed ordinal variables.[4] Extensions of this approach are available for sets of dichotomous variables (i.e. tetrachoric),[5] ordinal and continuous variables (i.e. polyserial),[6] and dichotomous and continuous variables (i.e. biserial).[6]

2.0.2.2 *Least squares and maximum likelihood*

2.0.2.2.1 Least squares

Least squares estimation in EFA models aims to minimize the sum of squared differences between observed and estimated correlation matrices, thereby minimizing the residuals of the fitted model.[7] This estimation approach was used in Cole et al.,[8] from which factor scores were based upon in **Chapter 4**.

2.0.2.2.2 Maximum likelihood

Maximum likelihood estimation of EFA models, as the name suggests, aims to (iteratively) maximize the likelihood of producing the observed correlation matrix, assuming the distribution of the variables (observed and latent) are multivariate normal.[2] This estimation approach was used in **Chapter 5** for all EFA models.

2.0.2.3 *Rotations*

Considering the formulation of the EFA model, there are an infinite number of possible solutions (i.e. EFA solutions are not unique); therefore, rotations are used to

better interpret the resulting factor loadings.[2,3] In this dissertation, where multiple factor models were considered, oblique rotations were used to allow factors to correlate (which for our applications in evaluating correlations among sinonasal symptoms and also sinonasal opacification, and their factors, was clearly the case rather than treating the resultant factors as uncorrelated [i.e. orthogonal] factors).

2.0.3 Factor scores and their estimation

2.0.3.1 *Factor scores, defined*

In the simplest sense, factor scores are estimated factor values which seek to distill the fitted factor analysis model into usable continuous variables, often in subsequent regression analysis.[9]

2.0.3.2 *Factor scores, estimated*

There are several approaches to estimation of factor scores, including Thurstone (i.e. regression),[10] Bartlett,[11] and item response theory (IRT)-based scores.[12] In this dissertation, we estimated IRT-based scores via the expected *a posteriori* (EAP) method.[13] The explicit details of EAP theta (θ; factor score) estimation are beyond the scope of this dissertation and will only briefly be covered. Theta estimation is an iterative procedure in which Newton-Raphson numerical integration is applied to the fitted EFA model in order to obtain the best estimate of theta, given the patterns of responses used as inputs to the EFA. This maximum likelihood-based estimate of theta is then combined with a normal prior distribution, thus resulting in an estimate of the mean of the combined posterior distribution.[13]

2.1 Chapter 5: Latent class analysis

2.1.1 Concept and utility

Latent class analysis (LCA) is a statistical method in which patterns of responses to a set of categorical variables are used to identify mutually exclusive and homogeneous subgroups (i.e. classes).[1] In **Chapter 5**, we applied LCA to binary indicators of opacification in six sinonasal regions in order to answer these two questions:

1) Does sinus opacification occur randomly in the different locations, or are there subgroups of subjects who evidence site-specific patterns of opacification?

2) If there are identifiable subgroups, how many are best represented by the data?

2.1.2 Estimation procedure

2.1.2.1 *Maximum likelihood*

The general form of the LCA model is provided below (**Equation 2.1.2.1.1**).[14]

Equation 2.1.2.1.1. General form of LCA model. Adapted from Collins LM. Latent Class and Latent Transition Analysis With Applications in the Social, Behavioral, and Health Sciences. In: Lanza ST, ed. Hoboken :: John Wiley & Sons, 2010.

$$P(Y = y) = \sum_{C=1}^{C} \gamma_C \prod_{j=1}^{J} \prod_{r_{j=1}}^{R_j} p_{j,r_{j\,|\,c}}^{I(y_j = r_j)}$$

In **Equation 2.1.2.1.1**, Y_j is a variable with R_j categories taking generic value $r_j = 1,...R_j$; $I(y_j = r_j)$ represents a binary variable that is equal to 1 when variable $j = r_j$, and 0 otherwise; γ_C represents the probabilities of membership in each latent class; and p represents the probability of observing a particular response conditional on latent class membership (c).[14] Model parameters are estimated by maximum likelihood estimation via an expectation-maximization algorithm,[15] with the exact likelihood function being maximized defined as the product over individuals of the likelihood components given the equation just above.

2.1.2.2 *Goodness of fit*

There are several absolute and relative measures of model fit useful in guiding the best LCA solution (i.e. the appropriate number of latent classes to extract). While not an exhaustive list, we briefly summarize the tests and indices used in **Chapter 5**.

2.1.2.2.1 Akaike's information criterion

Akaike's information criterion (AIC) is simply expressed as -2LL + 2*m*, where LL is the log-likelihood from the estimated model and *m* is the number of estimated parameters, with lower values indicating better model fit.

2.1.2.2.2 Bayesian information criterion

Similar to AIC, Bayesian information criterion (BIC) is -2LL + m * ln(n), where LL and m are the same as above and n is the sample size (i.e. number of observations).

2.1.2.2.3 Vuong-Lo-Mendell-Rubin likelihood ratio test

The Vuong-Lo-Mendell-Rubin (VLMR) likelihood ratio test (LRT) addresses the issue of non-nested models for which traditional LRT approaches faulter.[16,17] In brief, VLMR uses the derivatives from a k class model and k-1 class model to compute the p-value associated with the difference in log-likelihoods from these models. If the p-value is not significant (i.e. $p \geq 0.05$), then the null hypothesis of k-1 class model being appropriate is failed to be rejected. Said differently, a significant p-value (i.e. $p < 0.05$) would reject the null hypothesis and favor the model with a higher number of latent classes.

2.1.2.2.4 Bootstrapped likelihood ratio test

The bootstrapped LRT (BLRT) similarly addresses the issue of non-nested models by a series of four steps: 1) the k and k-1 class models are estimated and -2LL is calculated; 2) a bootstrap sample is generated from the k-1 class model and -2LL is calculated (by using estimated k class model in step 1); 3) this process is repeated several hundred times (we used 500 bootstrap samples in **Chapter 5** analyses) allowing estimation of the "true" distribution of -2LL; and 4) the p-value is obtained by comparing the "true" distribution in step 3 to the -2LL calculated in step 1.[18] As with VLMR, a significant p-value would indicate rejection of the null hypothesis that the k-1 class model is sufficient, therefore favoring the k class model.

2.1.3 Checking for local maxima

A well-known problem in LCA is that of local maxima in the likelihood.[19] Given the estimation procedure, it is possible for local solutions to be obtained, as opposed to global solutions. A local maximum solution is the best solution in a neighborhood of the parameter space, but not the global maximum. We used several strategies to more confidently assert that our final LCA model in **Chapter 5** was a global solution (i.e. best

fitting model). We first used several thousand random starts (5,000) in the first step of the estimation procedure and the best 500 in the second step. Next, after being assured that the model converged, we estimated the model again, but this time using twice as many random starts (first and second step) to determine if we converged to the same solution. Then, we assessed solutions for five of the starts (using their “seeds”) that had the same log-likelihood as the final model, to ensure that the solutions were the same.

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Chapter 3: Prevalence, severity, and risk factors for acute exacerbations of nasal and sinus symptoms by chronic rhinosinusitis status

3.0 Cover page

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3.1 Abstract

Background: Nasal and sinus symptoms (NSS) are common to many health conditions, including chronic rhinosinusitis (CRS). Few studies have investigated the occurrence and severity of, and risk factors for, acute exacerbations of NSS (AENSS) by CRS status (current, past, or never met European Position Paper on Rhinosinusitis [EPOS] criteria for CRS).

Methods: Four seasonal questionnaires were mailed to a stratified random sample of Geisinger primary care patients. Logistic regression was used to identify individual characteristics associated with AENSS occurrence and severity by CRS status (current long-term, current recent, past, never) using EPOS subjective symptoms-only ($EPOS_S$) CRS criteria. We operationalized three AENSS definitions based on prescribed antibiotics or oral corticosteroids, symptoms, and symptoms with purulence.

Results: Baseline and at least one follow-up questionnaires were available from 4,736 subjects. Self-reported NSS severity with exacerbation was worst in the current long-term CRS group. AENSS was common in all subgroups examined and generally more common among those with current $EPOS_S$ CRS. Seasonal prevalence of AENSS differed by AENSS definition and CRS status. Associations of risk factors with AENSS differed by definition, but CRS status, body mass index, asthma, hay fever, sinus surgery history, and winter season consistently predicted AENSS.

Conclusions: In this first longitudinal, population-based study of three AENSS definitions, NSS and AENSS were both common, sometimes severe, and differed by $EPOS_S$ CRS status. Contrasting associations of risk factors for AENSS by the different definitions suggest a need for a standardized approach to definition of AENSS.

3.2 Introduction

There are few prior longitudinal studies of nasal and sinus symptoms (NSS) and their acute exacerbation (AENSS) in general population samples and no standardized approaches to measurement of AENSS in epidemiologic studies. NSS are common to multiple health conditions, can be relapsing and remitting, can become chronic as in the case of chronic rhinosinusitis (CRS), and have a significant individual and population impact.[1-8] The European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) has operationalized a clinical definition of CRS, requiring both subjective symptoms which must be present for 12 continuous weeks and objective confirmation of sinonasal mucosal inflammation (e.g. via sinus computed tomography [CT]). For epidemiologic studies, EPOS only requires the presence of subjective symptoms (we designate as $EPOS_S$).[1,2]

Difficulties in obtaining objective evidence of inflammation have been an impediment to large-scale, population-based epidemiologic studies. Depending on individual characteristics, onset, duration, and season, the sudden onset or worsening of NSS could be an indication for allergic rhinitis (AR), acute rhinosinusitis (ARS), an acute exacerbation of chronic rhinosinusitis (AECRS), or other related diagnoses. Published studies of exacerbation among CRS patients have primarily focused on bacteriology,[9-11] immunology,[12,13] and medical treatments,[14-17] as opposed to population-based occurrence, severity, risk factors, and natural history. The International Consensus Statement on Allergy and Rhinology (ICAR), therefore, has declared a need for prevalence estimates of AECRS and more prospective studies, especially those which compare several definitions of AECRS.[2]

As such, the objectives of this study were to evaluate and compare seasonal prevalence of AENSS by $EPOS_S$ CRS status (hereafter CRS status) across three

definitions of AENSS; describe NSS severity by CRS and AENSS status; and identify self-reported individual characteristics associated with AENSS by CRS status. We addressed these objectives in a population-based longitudinal study using a sample of primary care patients from Geisinger who are representative of the general population in the area of central and northeastern Pennsylvania.

3.3 Materials and methods

3.3.1 Study overview

Details of the study design have been published elsewhere.[5,18] Briefly, in 2014, adult (at least 18 years of age) primary care patients were selected from the EHR of Geisinger to participate in a study of the epidemiology of CRS. Individuals who responded to the baseline questionnaire were additionally mailed four seasonal follow-up questionnaires over the course of 16-months, to evaluate seasonal exacerbations (**Table 3.3.1.1**; for example questionnaire see Supplemental material **Figure 3.7.1**). This study was approved by the Institutional Review Board (IRB) of Geisinger, which has an IRB Authorization Agreement with the Johns Hopkins Bloomberg School of Public Health. Health Insurance Portability and Accountability Act authorization and written informed consent waivers were approved by the IRB.

Table 3.3.1.1. Description of longitudinal questionnaires and number of responders

Description	April 2014	October 2014	February 2015	May 2015	August 2015
Questionnaire	Baseline	Fall Exacerbation	Winter Exacerbation	Spring Exacerbation	Summer Exacerbation
Mailings	3 (to August 2014)	2 (to January 2015)	1	1	2 (to December 2015)
Items	94	87	15	15	79
Sections		AENSS exacerbation	AENSS exacerbation	AENSS exacerbation	AENSS exacerbation
		CRS treatment (4wk)	CRS treatment (4wk)	CRS treatment (4wk)	CRS treatment (4wk)
	Current CRS	Current CRS			Current CRS
	Secondary CRS	Secondary CRS*			Secondary CRS
	Minor symptoms	Minor symptoms			Minor symptoms
	Doctor diagnoses	Anxiety			Work exposures and impacts
	Socioeconomic status	Depression symptoms			SHS and farm contacts
Responders	7847	4966	5094	4089	4600

Abbreviations: CRS = chronic rhinosinusitis; SES = socioeconomic status; SHS = second-hand smoke

*Secondary CRS indicates more specific questions about NSS frequency and severity not included as part of the diagnostic criteria for CRS

3.3.2 Study population

Geisinger provides primary care services to over 450,000 patients, with the majority residing in central and northeastern Pennsylvania. The source population for this study consisted of 200,769 adult primary care patients who had available EHR data, including race/ethnicity. Stratified sampling was utilized to over represent individuals more likely to have CRS, as well as racial/ethnic minorities (8% of Geisinger patients identify as non-white race/ethnicity). From the source population, 23,700 individuals were selected to participate in the baseline survey and baseline responders (n = 7847) were mailed four follow-up questionnaires with four-month intervals in-between (**Table 3.3.1.1**).

3.3.3 Description of sampling method

The sampling method has been reported previously.[5,18] Briefly, individuals with a greater likelihood of having CRS were over-sampled by using EHR data to categorize individuals into three groups, based on International Classification of Disease (ICD)-9 codes as well as Current Procedural Terminology (CPT) codes from patient medical records for: CRS, asthma, allergic rhinitis, sinus procedures, and related information.[18] Oversampling of racial and ethnic minorities was also performed. Sampling proportions are reported elsewhere.[5]

3.3.4 CRS classification

Individuals were classified as having $EPOS_S$ CRS as previously reported.[5,18] In brief, CRS status was determined using subject responses concerning the frequency of the cardinal symptoms of CRS (nasal congestion/blockage, green/yellow nasal discharge [purulence], post-nasal drip, smell loss, facial pain, and facial pressure), as defined by EPOS.[1] Based on responses to these questions at the baseline and first follow-up questionnaires, subjects were classified as “current long-term” (current CRS at both questionnaires), “current recent” (past or never CRS at baseline, current CRS at follow-up), “past” (past CRS at baseline, not current at follow-up) or “never” (no CRS at either

questionnaire). Only these questionnaires were used for determining CRS status in this study because two of the follow-up questionnaires (winter and spring exacerbation) did not include questions about EPOS symptoms over the past three months and we did not want to induce reverse causality in the association of CRS status and exacerbation. We did not differentiate between CRS with and without nasal polyps since objective evidence of CRS was unavailable for all study participants and therefore no way to reliably phenotype these subjects.

3.3.5 Operationalization of NSS severity and AENSS

NSS severity was assessed in two different ways. The first used self-reported rating of NSS on a 10-point visual analog scale while the second used self-report of having "worse" or "much worse" NSS on a five-point Likert scale.[1]

Using consensus recommendations[1,2] and prior evidence on CRS exacerbations[9-11,13,15,19] we operationalized three definitions for the classification of AENSS (see Supplemental material **Table 3.7.1**). All definitions required participants to self-report worsened NSS in the past four weeks. "AENSS-Med" defined exacerbation was based on self-reported medication use for worsened NSS. We only used antibiotics and oral corticosteroids as qualifying medications as these are unlikely to be prescribed for viral infections, thereby minimizing potential misclassification of AENSS as common colds. This definition is also parallel to the medical management recommended for asthma control,[1] since no evidence-based treatment recommendations exist for AECRS.[2] We did not include inhaled corticosteroids because this would certainly misclassify AENSS as asthma exacerbations. "AENSS-Sx" was based on duration (≥ 1 week) of worsened aggregate NSS, again to minimize ascertainment of colds as AENSS, since these usually resolve within 1 week. Lastly, "AENSS-Sx-Pur" required the same criteria as "AENSS-Sx", but additionally required self-reported worsened purulence in the past four weeks, yielding a definition with greater relative specificity. Although NSS could be

worse for longer than four weeks, only a four week period was measured on questionnaires.

3.3.6 Evaluation of risk factors for AENSS and confounding variables

Based on previous studies,[5,18] potential risk factors and confounding variables from the EHR included: current age (years); sex; race/ethnicity (white non-Hispanic vs. all other groups); smoking status (current, former, and never); body mass index (BMI, kg/m^2); Charlson comorbidity index[20]; and history of receiving Medical Assistance, a surrogate for family socioeconomic status (SES)[21]. Individual self-reported information was ascertained from baseline and follow-up questionnaires (**Table 3.3.1.1**).

Previous studies have shown asthma to be associated with CRS[5,22,23], and was therefore hypothesized to be a risk factor for AENSS. As such, individuals who experienced ≥ 1 asthma symptom (awakening at night due to wheezing; wheezing, chest tightness, or whistling in the chest when not having cold or flu; chest wheezing during or after exercise; dry cough at night apart from a cold or chest infection) at least some of the time were classified as having asthma symptoms at baseline. Migraine headaches have similarly been associated with CRS,[5,18] therefore a binary indicator for whether a subject had migraine headaches at baseline was determined as previously reported.[18,24] The continuous "Anxiety Sensitivity Index (ASI)"[25] measures how much a person fears the symptoms of anxiety, believing them to be harmful, and was created from the fall exacerbation questionnaire and included in the analysis as quintiles to help control for confounding due to an individual's propensity to be aware of and/or over-report symptoms. Questionnaire return dates were used to define the season in which exacerbations occurred as follows: autumn, September 22 through December 21; winter, December 22 through March 21; spring, March 22 through June 21; and summer, June 22 through September 21.

3.3.7 Statistical analyses

Given the paucity of information regarding NSS and AENSS by $EPOS_S$ CRS status, the goals of the analysis were to 1) assess differences in NSS severity by CRS status and AENSS definition, 2) estimate the seasonal prevalence of different subgroups of AENSS (e.g., by CRS status and AENSS definition) in the source population, and 3) evaluate associations of individual self-reported risk factors and season with AENSS by CRS status.

Survey-corrected methods were used for all analyses to account for the sampling design. Design weights were the inverse product of the probability of being selected into the study and probability of responding to the baseline questionnaire. Additionally, survey weights were corrected for attrition by estimating inverse probability of censoring weights (IPCW; see Supplemental material **Equation 3.7.1**). Since CRS status was not ascertained at all time-points, CRS status at the first follow-up questionnaire was used for all follow-up questionnaires. Subjects who skipped a questionnaire (23.9%) were excluded from all subsequent questionnaires to avoid intermittent missingness.

Risk factor analysis consisted of inverse-probability-weighted generalized estimating equations logistic regression models assuming an independence working correlation matrix and incorporated stabilized truncated survey weights. Final survey weights had a median of 2.81 and range 2.45 – 43.03. Taylor linearization was used to estimate robust variances and standard errors. Lastly, item non-response for covariates was addressed by using multiple imputation by chained equations (25 imputed data sets).

Covariates were identified as being a risk factor if they retained statistical significance in adjusted models and were not *a priori* determined to be a confounder. Methods for assessing model fit are limited in multiply-imputed survey-based regression models. However, model-fit was assessed by visual inspection of deviance residuals versus

predicted probabilities (from weighted candidate final models) and using. Archer-Lemeshow tests for goodness of fit. To assess the utility of the multiple imputations, Monte Carlo error estimates were generated for all effect estimates and associated test statistics. All analyses were conducted in STATA 14.1 (StataCorp, College Station, Texas).

3.4 Results

3.4.1 Description of participants

Baseline characteristics of the study population have been described elsewhere.[5,18] A total of 558 current long-term, 273 current recent, 1,644 past, and 2,261 never $EPOS_S$ CRS individuals contributed at least one observation to the analysis (**Table 3.4.1.1**). The general trends in **Table 3.4.1.1** suggests individuals with AENSS appeared to be younger, white, female, on medical assistance, and have greater Charlson comorbidity index values, compared to those without AENSS (**Table 3.4.1.1**). The prevalence of AENSS increased from the lowest in the never group, to intermediate in the past and current recent CRS groups, to the highest in the current long-term CRS status group (**Table 3.4.1.1**). AENSS recurrence, as identified through the four follow-up questionnaires, was the least common in the never group and the most common in the current long-term CRS group (see Supplemental material **Table 3.7.2**).

Table 3.4.1.1. Percentage (95% CI) of respondents and mean value (i.e., age, BMI) who ever met criteria for AENSS by operational criteria and by covariates[a]

	AENSS-Med[b]		AENSS-Sx[c]		AENSS-Sx-Pur[d]	
Characteristic	**Never Exacerbation**	**Ever Exacerbation**	**Never Exacerbation**	**Ever Exacerbation**	**Never Exacerbation**	**Ever Exacerbation**
$EPOS_S$ CRS status[e]						
Current long-term, n = 558	74.1 (65.2 – 83.0)[f]	25.9 (17.0 – 34.8)	41.7 (31.0 – 52.5)	58.3 (47.5 – 69.0)	74.6 (67.0 – 82.5)	25.2 (17.5 – 33.0)
Current recent, n = 273	80.8 (71.9 – 89.8)	19.2 (10.2 – 28.1)	48.9 (35.4 – 62.4)	51.1 (37.6 – 64.6)	84.2 (77.5 – 91.0)	15.8 (9.04 – 22.5)
Past, n = 1,644	84.4 (80.9 – 87.9)	15.6 (12.1 – 19.1)	50.9 (45.2 – 56.4)	49.2 (43.6 – 54.8)	79.4 (74.9 – 83.8)	20.6 (16.2 – 25.1)
Never, n = 2,261	92.4 (90.5 – 94.3)	7.62 (5.73 – 9.51)	71.1 (67.8 – 74.3)	28.9 (25.7 – 32.2)	89.4 (87.1 – 91.6)	10.6 (8.38 – 12.9)
p-value[g]		**< 0.001**		**< 0.001**		**< 0.001**
Age (years), mean	55.9 (54.8 – 56.9)	53.3 (50.7 – 55.9)	57.1 (55.8 – 58.4)	52.9 (51.4 – 54.5)	56.5 (55.4 – 57.5)	50.2 (47.8 – 52.6)
p-value		0.08		**< 0.001**		**< 0.001**
Sex						
Male, n = 1,741	91.2 (88.7 – 93.7)	8.79 (6.29 – 11.3)	68.6 (64.2 – 73.0)	31.4 (27.0 – 35.8)	86.6 (83.4 – 89.9)	13.4 (10.1 – 16.6)
Female, n = 2,995	88.4 (86.3 – 90.5)	11.6 (9.51 – 13.7)	62.3 (27.0 – 65.8)	37.7 (34.2 – 41.1)	86.2 (83.8 – 88.5)	13.8 (11.5 – 16.2)
p-value		0.10		**0.03**		0.82
Race/ethnicity						
White, n = 4,399	89.3 (87.6 – 91.0)	10.7 (9.01 – 12.4)	64.2 (61.4 – 67.0)	35.8 (33.0 – 38.6)	86.1 (84.1 – 88.1)	13.9 (11.9 – 15.9)
Non-white, n = 337	91.6 (88.8 – 94.4)	8.38 (5.56 – 11.2)	73.9 (68.6 – 79.1)	26.1 (20.9 – 31.4)	91.5 (88.4 – 94.5)	8.54 (5.50 – 11.6)
p-value		0.19		**< 0.01**		**0.011**

Medical Assistance[h]						
Never received, n = 4,328	89.9 (88.2 – 91.6)	10.1 (8.44 – 11.8)	64.6 (61.8 – 67.4)	35.4 (32.6 – 38.2)	86.6 (84.6 – 88.6)	13.4 (11.4 – 15.4)
Ever received, n = 408	84.0 (77.4 – 90.5)	16.0 (9.52 – 22.6)	64.6 (54.7 – 74.5)	35.4 (25.5 – 45.3)	83.7 (76.5 – 90.8)	16.3 (9.19 – 23.5)
p-value		**0.04**		1.00		0.41
Body mass index (BMI; kg/m^2), mean	29.3 (28.9 – 29.7)	30.6 (29.4 – 31.8)	29.6 (29.0 – 30.1)	29.2 (28.6 – 29.8)	29.4 (29.0 – 29.9)	29.5 (28.5 – 30.5)
p-value		0.05		0.45		0.79
Charlson comorbidity index, mean	1.10 (1.04 – 1.16)	1.39 (1.20 – 1.58)	1.10 (1.02 – 1.18)	1.19 (1.09 – 1.29)	1.13 (1.06 – 1.19)	1.15 (1.00 – 1.30)
p-value		**< 0.01**		0.20		0.83
Smoking status						
Current, n = 581	87.1 (82.0 – 92.1)	12.9 (7.86 – 18.0)	64.5 (56.3 – 72.7)	35.5 (27.3 – 43.7)	88.2 (83.2 – 93.3)	11.8 (6.69 – 16.8)
Former, n = 1,460	91.4 (88.9 – 93.9)	8.62 (6.14 – 11.1)	65.9 (61.0 – 70.7)	34.1 (29.3 – 39.0)	87.1 (83.6 – 90.6)	12.9 (9.43 – 16.4)
Never, n = 2,695	88.9 (86.6 – 91.1)	11.1 (8.87 – 13.4)	65.0 (60.4 – 67.5)	36.0 (32.5 – 39.6)	85.6 (83.0 – 88.1)	14.4 (11.9 – 17.0)
p-value		0.22		0.84		0.61

Abbreviations: CI = confidence interval; CRS = chronic rhinosinusitis; EHR = electronic health record; EPOS = European Position Paper on Rhinosinusitis; SES = socioeconomic status

[a] Unless otherwise noted, estimates are row percentages (within characteristic) of ever/never having an AENSS during follow-up

[b] AENSS-Med= worse/much worse NSS in past 4 weeks + use of systemic corticosteroids or antibiotic prescription for worsened NSS

[c] AENSS-Sx = worse/much worse NSS in past 4 weeks + worse over any time period up to 4 weeks + remained worse for ≥ 1-week

[d] AENSS-Sx-Pur = worse/much worse NSS in past 4 weeks + worse over any time period up to 4 weeks + remained worse for ≥ 1 week + worse/much worse purulence

[e] $EPOS_S$ CRS status determined using baseline and fall exacerbation questionnaires: current long-term CRS = EPOS epidemiologic criteria fulfilled at both questionnaires; current recent CRS = current CRS at fall questionnaire, but not at baseline; past CRS = EPOS epidemiologic criteria fulfilled in lifetime, but not during study; never CRS = EPOS epidemiologic criteria never met

[f] Population-estimates were derived by using survey-corrected methods with robust standard error estimation

[g] p-values represent differences in means (continuous variables) or Pearson's chi-square (categorical variables)

[h] Medical Assistance is a binary indicator of SES

3.4.2 Severity of nasal and sinus symptoms

Mean NSS severity scores varied by CRS group and exacerbation status (**Figure 3.4.2.1;** Supplemental material **Table 3.7.3**). There were statistically significant associations between CRS status and NSS severity (**Table 3.7.3**). Mean NSS scores increased ordinally from the lowest score in the never CRS group to the highest score in the current long-term CRS group, where those who were having AENSS had higher NSS severity than those who were not ($p < 0.001$ for all CRS status groups). Mean NSS

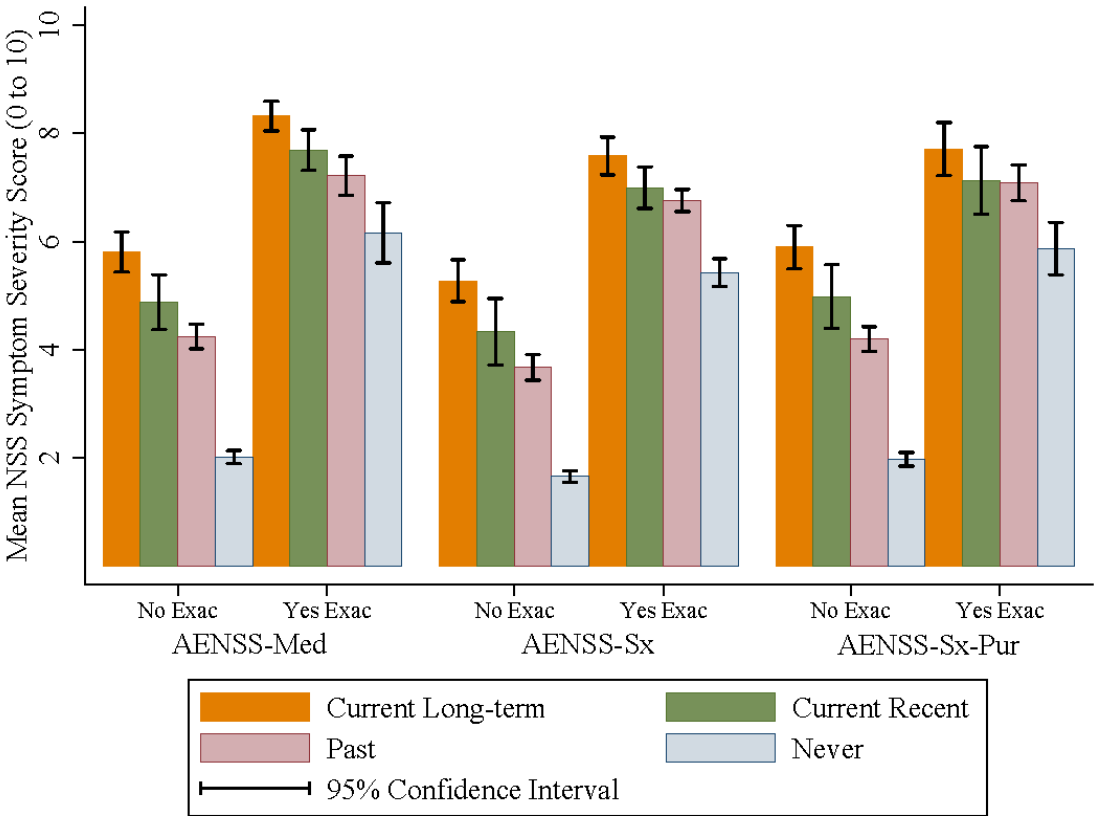

Figure 3.4.2.1. Mean nasal and sinus symptom severity score on a 10-point visual analogue scale, by EPOS$_S$ defined CRS status (current long-term, current recent, past, and never) and exacerbation definition. Nasal and sinus symptoms (NSS) severity in the past 4 weeks was ascertained by self-report at each follow-up questionnaire and estimated in the source population. Three definitions of AENSS were operationalized as follows: AENSS-Med, AENSS-Sx, and AENSS-Sx-Pur. Non-overlapping confidence intervals indicate statistical significance ($p < 0.05$). Exact p-values of pairwise statistical associations are displayed in Table 3.7.3.

severity scores by AENSS-Med and AENSS-Sx-Pur defined exacerbations were greater than in AENSS-Sx (**Figure 3.4.2.1**; Supplemental material **Table 3.7.3**).

3.4.3 Seasonal prevalence of AENSS

Prevalence estimates of AENSS by CRS status and AENSS definition were estimated for each season (**Figure 3.4.3.1;** Supplemental material **Table 3.7.4**). The seasonal peak prevalence for exacerbation consistently occurred in the winter for past CRS status and in spring for never CRS status. Seasonal trends were comparable between AENSS-Sx and -Sx-Pur for the current long-term and current recent CRS groups, with peak prevalence occurring in the winter for the current recent CRS group, and a modest peak in the summer for the current long-term CRS group (**Figure 3.4.3.1;** Supplemental material **Table 3.7.4**).

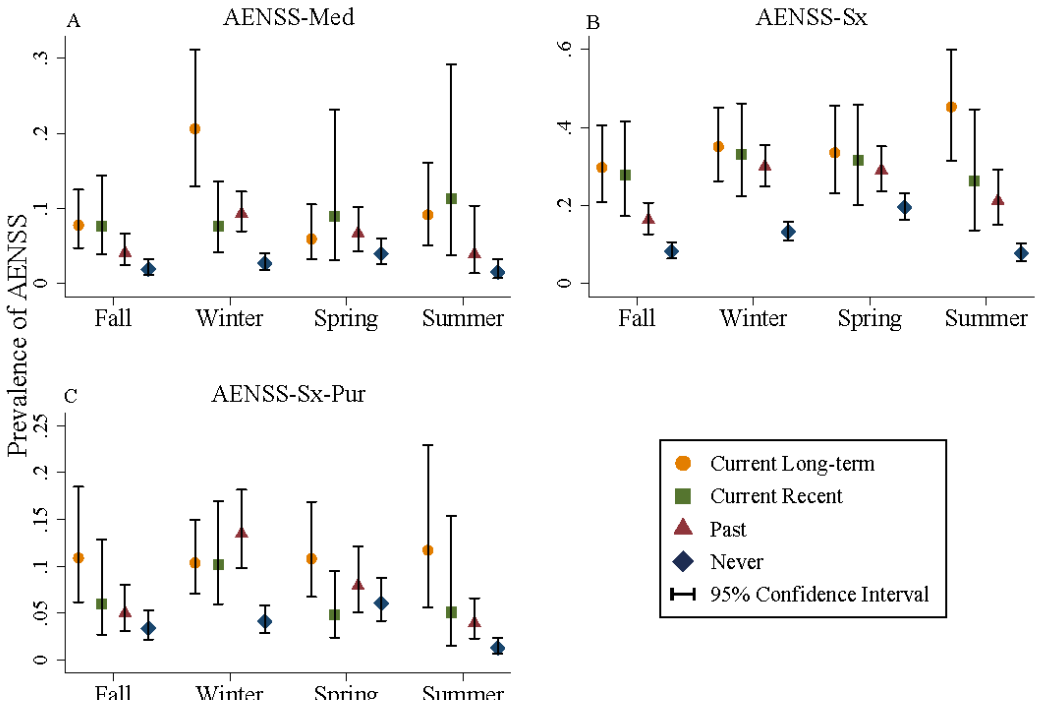

Figure 3.4.3.1. Population estimated prevalence of AENSS, by EPOSS defined CRS status (current long-term, current recent, past, and never), exacerbation definition, and season. Prevalence was estimated in the source population. Three definitions of AENSS were operationalized as follows: A, AENSS-Med; B, AENSS-Sx-Pur; C, AENSS-Sx-Pur.

3.4.4 Individual characteristic and seasonal risk factors for AENSS

Risk factor analysis proceeded with two of the three AENSS definitions (AENSS-Med and -Sx-Pur). We did not include AENSS-Sx since prevalence estimates were much greater from this definition compared to AENSS-Med and -Sx-Pur, which were both comparable, indicating a low relative specificity of AENSS-Sx compared to the other definitions. **Tables 3.4.4.1** and **3.4.4.2** show the adjusted odds ratios (aORs) and 95% CIs for several covariates estimated from logistic regression models.

Several significant and elevated odds ratios were identified in relation to AENSS-Med (**Table 3.4.4.1**) for higher BMI, being a current smoker, having asthma or migraine symptoms at baseline, doctor diagnosed hay fever, having had two or more sinus surgeries, and winter season. As CRS status was found to modify associations of season with AENSS-Med, associations are displayed within strata of CRS status (**Table 3.4.4.1**).

Elevated odds ratios of risk factors with AENSS-Sx-Pur (**Table 3.4.4.2**) were found for white race/ethnicity, BMI, having asthma symptoms at baseline, doctor diagnosed hay fever, history of having two or more sinus surgeries, and season (winter and spring). Age modified associations of CRS status with AENSS, therefore CRS status associations are displayed at the grand mean age (55.1 years). Subjects with either past or current long-term CRS had increased odds of AENSS-Sx-Pur. The interaction between age and CRS status was observed as a linear reduction in odds of AENSS-Sx-Pur with higher ages for all CRS status groups, except current long-term CRS (**Table 3.4.4.2**).

Table 3.4.4.1. Associations with exacerbation of nasal and sinus symptoms defined by AENSS-Med

Risk Factor[a]	Adjusted Odds Ratio (95% Confidence Interval)[b]
$EPOS_S$ CRS status[c]	
Never	
Fall	Ref
Winter	1.48 (0.91 – 2.41)
Spring	2.01 (1.22 – 3.32)**
Summer	0.80 (0.42 – 1.55)
Past	
Fall	1.28 (0.73 – 2.23)
Winter	3.73 (2.30 – 6.06)***
Spring	2.18 (1.27 – 3.75)**
Summer	0.94 (0.46 – 1.90)
Current recent	
Fall	2.97 (1.30 – 6.77)*
Winter	3.22 (1.59 – 6.51)**
Spring	2.64 (1.11 – 6.26)*
Summer	3.84 (1.33 – 11.07)*
Current long-term	
Fall	2.55 (1.41 – 4.62)**
Winter	5.96 (3.33 – 10.66)***
Spring	1.82 (0.89 – 3.74)
Summer	2.89 (1.43 – 5.84)**
Age (per five-year increase; years)	0.97 (0.93 – 1.02)
Sex	
Male	Ref
Female	1.35 (1.05 – 1.74)*
Race/ethnicity	
White	Ref
Non-white	0.66 (0.43 – 1.00)
Medical Assistance[d]	
Never received	Ref
Ever received	1.37 (0.91 – 2.06)
Body mass index (per 1 kg/m^2 increase; BMI; kg/m^2)	1.03 (1.02 – 1.05)***
Charlson comorbidity index (per 1 unit increase in index value)	1.09 (1.01 – 1.18)*
Smoking status (baseline)	
Never	Ref
Former	1.01 (0.77 – 1.32)
Current	1.53 (1.08 – 2.18)*
Asthma symptoms (baseline)	
None	Ref
At least one	1.47 (1.14 – 1.88)**
History of migraine symptoms (baseline)	
No	Ref
Yes	1.55 (1.17 – 2.06)**

Dr. diagnosed hay fever (baseline)	
No	Ref
Yes	1.36 (1.07 – 1.74)*
History of sinus surgeries (baseline)	
None	Ref
1	1.46 (1.04 – 2.05)*
2 or more	1.75 (1.11 – 2.76)*
Anxiety sensitivity index (quintiles)	
1	Ref
2	0.96 (0.65 – 1.42)
3	0.78 (0.52 – 1.17)
4	1.18 (0.80 – 1.75)
5	1.29 (0.89 – 1.87)

Abbreviations: AENSS = acute exacerbation of nasal and sinus symptoms; CRS = chronic rhinosinusitis; EHR = electronic health record; EPOS = European Position Paper on Rhinosinusitis; NSS = nasal and sinus symptoms

*p-value<0.05, **p-value<0.01, ***p-value<0.001

[a]Risk factors selected from the electronic health record (EHR) include: age, sex, race/ethnicity, receival of Medical Assistance, and body mass index (BMI). Risk factors from self-report includes: asthma symptoms, Dr. diagnosed hay fever, history and number of sinus surgeries, and anxiety sensitivity.

[b] Adjusted estimates from survey-corrected marginal logistic regression models with robust standard error estimation

[c] $EPOS_S$ CRS status determined using baseline and fall exacerbation questionnaires: current long-term CRS = EPOS epidemiologic criteria fulfilled at both questionnaires; current recent CRS = current CRS at fall questionnaire, but not at baseline; past CRS = EPOS epidemiologic criteria fulfilled in lifetime, but not during study; never CRS = EPOS epidemiologic criteria never met

[d] Medical Assistance is a binary indicator of socioeconomic status (SES)

[e] Season: Autumn = September 22 through December 21; Winter = December 22 through March 21; Spring = March 22 through June 21; Summer = June 22 through September 21

Table 3.4.4.2. Associations with exacerbation of nasal and sinus symptoms defined by AENSS-Sx-Pur

Risk Factor[a]	Adjusted Odds Ratio (95% Confidence Interval)[b]
$EPOS_S$ CRS status[c]	
Never	Ref
Past	1.56 (1.18 – 2.06)**
Current recent	1.56 (0.97 – 2.50)
Current long-term	2.33 (1.62 – 3.34)***
Age trend (per five-year increase; years)	
Never	0.85 (0.81 – 0.90)***
Past	0.92 (0.87 – 0.97)**
Current Recent	0.82 (0.71 – 0.94)**
Current Long-term	1.01 (0.93 – 1.10)
Sex	
Male	Ref
Female	1.09 (0.86 – 1.38)
Race/ethnicity	
White	Ref
Non-white	0.52 (0.34 – 0.79)**
Medical Assistance[d]	
Never received	Ref
Ever received	0.95 (0.67 – 1.35)
Body mass index (per 1 kg/m^2 increase; BMI; kg/m^2)	1.02 (1.01 – 1.03)**
Charlson comorbidity index (per 1 unit increase in index value)	0.94 (0.88 – 1.02)
Asthma symptoms (baseline)	
None	Ref
At least one	1.68 (1.32 – 2.15)***
History of migraine symptoms (baseline)	
No	Ref
Yes	1.34 (1.00 – 1.79)
Dr. diagnosed hay fever (baseline)	
No	Ref
Yes	1.36 (1.08 – 1.71)*
History of sinus surgeries (baseline)	
None	Ref
1	1.30 (0.95 – 1.78)
2 or more	1.58 (1.06 – 2.35)*
Anxiety sensitivity index (quintiles)	
1	Ref
2	1.00 (0.69 – 1.44)
3	0.92 (0.63 – 1.34)
4	1.19 (0.83 – 1.71)
5	1.36 (0.95 – 1.95)

Season[e]	
Fall	Ref
Winter	2.17 (1.67 – 2.82)***
Spring	1.71 (1.28 – 2.29)***
Summer	0.88 (0.62 – 1.25)

Abbreviations: AENSS = acute exacerbation of nasal and sinus symptoms; CRS = chronic rhinosinusitis; EHR = electronic health record; EPOS = European Position Paper on Rhinosinusitis; NSS = nasal and sinus symptoms

*p-value<0.05, **p-value<0.01, ***p-value<0.001

[a] Risk factors selected from the electronic health record (EHR) include: age, sex, race/ethnicity, receival of Medical Assistance, and body mass index (BMI). Risk factors from self-report includes: asthma symptoms, Dr. diagnosed hay fever, history and number of sinus surgeries, and anxiety sensitivity.

[b] Adjusted estimates from survey-corrected marginal logistic regression models with robust standard error estimation

[c] $EPOS_S$ CRS status determined using baseline and fall exacerbation questionnaires: current long-term CRS = EPOS epidemiologic criteria fulfilled at both questionnaires; current recent CRS = current CRS at fall questionnaire, but not at baseline; past CRS = EPOS epidemiologic criteria fulfilled in lifetime, but not during study; never CRS = EPOS epidemiologic criteria never met

[d] Medical Assistance is a binary indicator of socioeconomic status (SES)

[e] Season: Autumn = September 22 through December 21; Winter = December 22 through March 21; Spring = March 22 through June 21; Summer = June 22 through September 21

3.5 Discussion

To our knowledge, this is the first study of the epidemiology of AENSS by $EPOS_S$ CRS status, while evaluating three definitions of AENSS. There were several potentially important findings by season and CRS status, offering possible etiologic and diagnostic insights relevant to clinical management of AENSS. NSS and AENSS were common among all subjects; NSS and AENSS severity were worst in subjects with current, long-term CRS; prevalence of AENSS as measured by AENSS-Sx was almost 2-fold higher than by -Sx-Pur and -Med; there were clear seasonal prevalence differences observed using the different definitions of AENSS; and risk factor analysis showed differing associations depending on the definition of AENSS, particularly that odds of AENSS-Sx-Pur did not decline with increasing age in current long-term $EPOS_S$ subjects but did in all other $EPOS_S$ groups.

In the absence of consensus on how to measure AENSS, we operationalized three definitions that first identified worsening of symptoms (e.g., NSS in past four weeks reported as worse or much worse than "usual") and then applied criteria that would differentially maximize sensitivity (the proportion of people with an exacerbation who met the AENSS definition), positive predictive value (PPV; the proportion of people who met the AENSS definition who had an exacerbation), and clinical similarity to how asthma exacerbation is often defined in epidemiologic studies. AENSS-Sx was the most sensitive (and by definition, least specific) definition, and is useful for researchers wanting to estimate the prevalence of AENSS while avoiding under-estimation. Of the three definitions, AENSS-Sx-Pur should have the highest PPV, and therefore may be the best for risk factor analysis since its lower misclassification will minimize bias in effect estimates towards the null. Lastly, a medication-based AENSS definition (AENSS-Med) for CRS requires care-seeking behavior for symptoms that are generally not life-

threatening, thus making a medication-based definition much more reliant on health care access and delivery.

Although overall prevalence estimates for AENSS-Med and -Sx-Pur were comparable, there was little overlap in individuals ascertained by the two definitions, with only 31% of AENSS-Sx-Pur events additionally meeting criteria for AENSS-Med (see Supplemental material **Table 3.7.5**). Discordance could be due to AENSS-Med being influenced by an individual's propensity to seek and be provided with medical care.

AENSS occurred in all CRS status groups, but prevalence was higher and severity worse among subjects with past or current (long-term and recent) CRS. The absolute change in severity during an AENSS was largest among subjects who never met $EPOS_S$ CRS criteria, possibly due to a ceiling effect in NSS severity among individuals with current or past CRS.

AENSS prevalence was greatest in the winter and spring for the past and never CRS groups, respectively, across all three AENSS definitions. This suggests exacerbations might be driven by viral infections in the winter (e.g. rhinoviruses[26-30]) or seasonal allergens and allergic rhinitis, for those with or without a history of CRS, respectively. No consistent seasonal patterns of AENSS were observed for the current CRS status groups across all three definitions of AENSS; however, a peak prevalence occurred in the winter or summer (AENSS-Med and AENSS-Sx/Sx-Pur, respectively) for the current recent CRS group. Prevalence of AENSS-Med was greatest in the current long-term CRS status group and occurred in the winter season, yet no major seasonal changes in AENSS-Sx/Sx-Pur were observed for this group, apart from modest associations with summer season. This could be due to residual selection bias due to loss-to-follow-up unaccounted for by the weighting procedure, or could reflect specific seasonal triggers relevant to this subgroup (e.g. ragweed). It is possible that individuals with a long-term

history of current CRS are more likely to be prescribed medications for NSS in the winter, although NSS may not necessarily be more severe (given the lack of observed associations between season and AENSS-Sx/-Sx-Pur in this group). This may also reflect underlying pathobiology relevant to triggers of exacerbation in this group, since medical management would depend on the trigger (e.g. infections vs. grass pollen).

We identified clinical and seasonal factors associated with AENSS. CRS status, increased BMI, asthma symptoms, hay fever, migraine symptoms, history of sinus surgeries, and season were associated with AENSS by both Med and Sx-Pur defined exacerbation. Our findings with BMI are similar to those found previously with CRS[31,32] and other otorhinolaryngological[32] diseases, possibly due to chronic low-grade inflammation associated with obesity.[33,34] Asthma[1,2,22,23] and hay fever[1,2,22,23] have been associated with CRS; however, symptom overlap between these conditions could indicate measurement error in $EPOS_S$ criteria. To address this issue, we evaluated whether hay fever or asthma modified associations of CRS status with AENSS. As we found no evidence for this, we included hay fever and asthma diagnoses as covariates in regression models without further stratification and statistical significance suggests indication of the unified airways disease concept. The relationship between migraines and NSS has been observed in previous studies,[5,23] but could be due to misclassification of overlapping symptoms or biologic pathways, [35-37] or both. Sinus surgery was also associated with AENSS and could be due to bacterial infections in some CRS patients,[38] or be a proxy for individuals with recalcitrant CRS or persistent ARS, who are more likely to be aware of the severity of sinus symptoms over time.

Females were more likely to have AENSS-Med than males, possibly due to residual confounding associated with medical-seeking and -prescribing behaviors,[39] since this association was only modestly observed in the AENSS-Sx-Pur model; however, female

sex has been associated with CRS symptoms in other studies.[5,40,41] Non-white race/ethnicity was associated with reduced odds of both AENSS definitions, though only statistically significant in the AENSS-Sx-Pur model. Lastly, never smokers were less likely to have AENSS-Med, compared to current smokers, although no association with smoking status and AENSS-Sx-Pur was observed. The odds of AENSS-Sx-Pur declined with higher ages, excluding the current long-term CRS status group, possibly due to differential susceptibility to viral infections which precede bacterial infections and decrease with increasing age.[42] Yet, individuals with long-term CRS may be at risk of developing viral respiratory infections even at older ages due to compromised epithelial barrier function,[43,44] which can accompany CRS,[1,2,45] suggestive of a disease progressive model in those with persistent CRS.

Our study had several strengths, including study of the general population in the region representing the full spectrum of diseases with NSS, longitudinal design (the first to our knowledge), large sample size, and evaluation of a relevant set of individual-reported potential risk factors for AENSS, as well as season. We also used several definitions of AENSS to comparatively assess their utility in epidemiologic research, as advised by ICAR.[2] Our study is not without limitations, however. We used a definition of CRS which did not include confirmation of inflammation by endoscopy or CT scan so we were unable to classify individuals with clinical CRS. Second, both CRS status and self-reported individual characteristics were selected from the same questionnaires; as such there is the potential for spurious associations between them, since they are dependent on how an individual interprets and responds to the questions. However, a strength of this study is the inclusion of the ASI as a covariate, which adjusts for an individual's propensity to over-report symptoms and comorbidities. Therefore, the possibility of false

associations from same source bias was mitigated. Furthermore, we used weighting methods and multiple imputation to adjust for non-response and potential selection bias.

In summary, our study found that NSS and AENSS were common in the general population. NSS and AENSS severity were worse across categories of $EPOS_S$ CRS, peaking among current long-term CRS. Seasonal exacerbation prevalence depended on the AENSS definition and differed by $EPOS_S$ CRS status. Results suggest that a high PPV definition (e.g., AENSS-Sx-Pur) may provide the best balance between a sensitive definition and one which is clinically meaningful.

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3.7 Supplemental material

Study ID_____

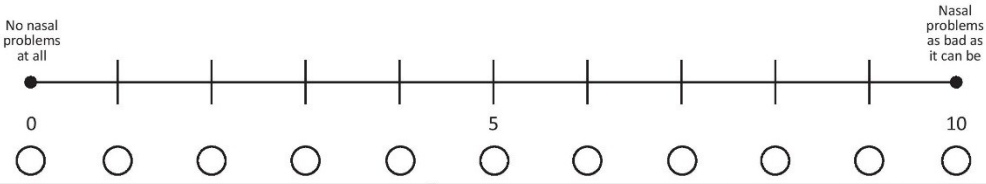
Thank you for your continued contributions to the chronic rhinosinusitis study of your nasal and sinus symptoms. We are contacting you now because we want to understand how symptoms might change with the seasons. We hope you will continue to complete these surveys. **This one is much shorter, less than one page.** Thank you for your time!

Population Study of Nasal and Sinus Symptoms-Exacerbations

Complete this survey in one sitting. It should take around 5 minutes. Use a pen, fill in the circle completely. Answer each question as best you can. Please return the survey in the self-addressed stamped envelope. Thank you for your participation and help!

The next questions are about how your symptoms have been over the past four weeks.

1. Mark an X in the circle below the number that indicates how severe your nasal and sinus symptoms have been over the last four weeks.



2. My nasal problems in the past 4 weeks have been...
   - ○ Much better than usual (You are done. Thank you!)
   - ○ Better than usual (You are done. Thank you!)
   - ○ About the same (You are done. Thank you!)
   - ○ Worse than usual (Continue)
   - ○ Much worse than usual (Continue)

If your nasal problems are better than usual or about the same, you are done. No need to continue.

3. In the past four weeks, my nasal problems...
   - ○ Got worse over two to four weeks
   - ○ Got worse over one to two weeks
   - ○ Got worse in a week or less

4. How long have your nasal problems in the past four weeks been worse than usual?
   - ○ Less than a week
   - ○ 1 to 2 weeks
   - ○ More than 2 weeks

Check the answer that describes how each nasal problem has changed over the past 4 weeks.

		Much better than usual	Better than usual	About the same	Worse than usual	Much worse than usual
5	Blockage of your nasal passages (nasal congestion)	○	○	○	○	○
6	Nasal discharge that was yellow or green in color	○	○	○	○	○
7	Post-nasal drip	○	○	○	○	○
8	Loss of sense of smell	○	○	○	○	○
9	Facial pain	○	○	○	○	○
10	Facial pressure	○	○	○	○	○

Please indicate if you have taken any of the following actions for your worse than usual nasal and sinus symptoms in the past four weeks.

11	Saw or called your doctor?	○ Yes	○ No
12	Used steroid pills?	○ Yes	○ No
13	Used antibiotics?	○ Yes	○ No
14	Used nasal steroid spray?	○ Yes	○ No
15	Used over the counter cold/allergy pills?	○ Yes	○ No

Figure 3.7.1. Example questionnaire used to operationalize AENSS definitions.

Table 3.7.1. Definitions for acute exacerbations of nasal and sinus symptoms (AENSS)

Definition	Medication Use[a]	Duration of Symptoms[b]	Symptom(s) Required[c]
AENSS-Med[d]	Any systemic corticosteroid or antibiotic prescription	-	-
AENSS-Sx[e]	-	≥1 week	-
AENSS-Sx-Pur[f]	-	≥1 week	Worse green/yellow discharge (purulence)

Abbreviations: AENSS = acute exacerbation of nasal and sinus symptoms; CRS = chronic rhinosinusitis; NSS = nasal and sinus symptoms

[a] Use of medications, including systemic corticosteroids and/or oral antibiotics, ascertained by self-report on each follow-up questionnaire

[b] Timing of duration for worse/much worse NSS ascertained by self-report on each questionnaire from individuals who indicated worse/much worse NSS in past 4 weeks

[c] Specifics for severity of cardinal CRS symptoms ascertained by self-report on each questionnaire from individuals who indicated worse/much worse NSS in the past 4 weeks

[d] AENSS-Med = worse/much worse NSS in past 4 weeks + use of systemic corticosteroids or antibiotic prescription for worsened NSS

[e] AENSS-Sx = worse/much worse NSS in past 4 weeks + worse over any time period up to 4 weeks + remained worse for ≥ 1-week

[f] AENSS-Sx-Pur = worse/much worse NSS in past 4 weeks + worse over any time period up to 4 weeks + remained worse for ≥ 1 week + worse/much worse purulence

Equation 3.7.1. Inverse probability of censoring weights (IPCW).

IPCWs were calculated by using predicted probabilities from a pooled logistic regression model, in which the outcome (rij) was odds of remaining in the study at time t, and included a vector of baseline covariates (Zi0): age (centered), age2 (centered), sex, race/ethnicity, history of Medical Assistance, time (follow-up visit), Charlson comorbidity index (centered), as well as CRS status at the previous time-point (lagged CRS status; Zij-1). CRS status was only determined at two of the follow-up questionnaires (fall and summer exacerbation). As such, CRS status at the fall exacerbation questionnaire was carried forward until the summer exacerbation questionnaire. To account for large weights, which can lead to model instability, we used stabilized IPCWs. The stabilizing factor of the IPCW used as the numerator all baseline covariates included in original IPCW model, with the exclusion of age^2 (Zio*).

$$Stabilized\ IPCW = \frac{\Pr(r_{ij} = 1 \mid Z_{i0}^{*})}{\Pr(r_{ij} = 1 \mid Z_{i0} + Z_{ij-1})}$$

The survey weights for these analyses were a product of the stabilized IPCW and a truncated design weight (where the strata with the largest weights were truncated to the next highest category), to further reduce model instability from extreme weights.

$$Survey\ weight = \frac{\Pr(r_{ij} = 1 \mid Z_{i0})}{\Pr(r_{ij} = 1 \mid Z_{i0} + Z_{ij-1})}\ X\ Design\ weight_i$$

Table 3.7.2. Proportion (column percentages and 95% confidence intervals)[a] of recurrent AENSS events identified during four follow-up questionnaires

$EPOS_S$ CRS status[b]	AENSS-Med[c]	AENSS-Sx[d]	AENSS-Sx-Pur[e]
Current long-term, n = 558			
0	74.1 (64.2 – 82.0)	41.7 (31.5 – 52.7)	74.5 (66.2 – 81.7)
1	21.1 (13.6 – 31.1)	32.2 (23.2 – 42.7)	20.7 (14.2 – 29.0)
2	3.27 (1.88 – 5.62)	15.0 (9.20 – 23.6)	3.34 (1.92 – 5.76)
3 or 4	1.55 (0.58 – 4.08)	11.0 (6.66 – 17.8)	1.23 (0.53 – 2.83)
Current recent, n = 273			
0	80.8 (70.3 – 88.3)	48.9 (35.8 – 62.1)	84.2 (76.3 – 89.9)
1	11.2 (6.80 – 18.0)	23.3 (13.9 – 36.5)	11.8 (7.12 – 19.0)
2	7.10 (2.47 – 18.8)	17.1 (10.1 – 27.5)	2.76 (1.20 – 6.23)
3 or 4	0.84 (0.14 – 4.89)	10.7 (4.93 – 21.6)	1.21 (0.21 – 6.73)
Past, n = 1,644			
0	84.4 (80.6 – 87.6)	50.8 (45.2 – 56.4)	79.4 (74.6 – 83.5)
1	13.2 (10.3 – 16.8)	33.2 (28.1 – 38.7)	17.6 (13.7 – 22.3)
2	2.15 (1.04 – 4.42)	11.4 (8.64 – 14.9)	2.82 (1.66 – 4.75)
3 or 4	0.25 (0.15 – 0.40)	4.64 (3.08 – 6.94)	0.19 (0.12 – 0.31)
Never, n = 2,261			
0	92.4 (90.3 – 94.1)	71.1 (67.7 – 74.2)	89.4 (86.9 – 91.4)
1	7.14 (5.49 – 9.24)	21.1 (18.3 – 24.3)	9.81 (7.81 – 12.3)
2	0.43 (0.19 – 0.98)	5.86 (4.47 – 7.65)	0.39 (0.23 – 0.65)
3 or 4	0 (0 – 0.22)	1.95 (1.21 – 3.15)	0.45 (0.15 – 1.39)

Abbreviations: AENSS = acute exacerbation of nasal and sinus symptoms; CRS = chronic rhinosinusitis; EPOS = European Position Paper on Rhinosinusitis; NSS = nasal and sinus symptoms

[a] Column percentages estimated by survey-corrected methods and robust standard error estimation
[b] $EPOS_S$ CRS status determined using baseline and fall exacerbation questionnaires: current long-term CRS = EPOS epidemiologic criteria fulfilled at both questionnaires; current recent CRS = current CRS at fall questionnaire, but not at baseline; past CRS = EPOS epidemiologic criteria fulfilled in lifetime, but not during study; never CRS = EPOS epidemiologic criteria never met
[c] AENSS-Med = worse or much worse NSS in past 4 weeks and treated with either oral corticosteroids or antibiotics for worsened symptoms
[d] AENSS-Sx = worse or much worse NSS in past 4 weeks and worsened symptoms lasting 1 week or more
[e] AENSS-Sx-Pur = worse or much worse NSS in past 4 weeks, worsened symptoms lasting 1 week or more, and one of worsened symptoms was green/yellow nasal discharge (mucopurulence)

Table 3.7.3. Figure 1 estimates[a] of nasal and sinus symptom severity in the past four weeks; by $EPOS_S$ CRS status and definition of exacerbation ("Exac")

$EPOS_S$ CRS status [a]	AENSS-Med[b]		AENSS-Sx[c]		AENSS-Sx-Pur[d]	
	No Exac	Exac	No Exac	Exac	No Exac	Exac
Current long-term, n = 558	5.81 (5.44 – 6.18)	8.32 (8.05 – 8.59)***	5.27 (4.89 – 5.66)	7.58 (7.24 – 7.92)***	5.90 (5.50 – 6.29)	7.71 (7.25 – 8.18)***
Current recent, n = 273	4.88 (4.38 – 5.38)	7.69 (7.10 – 8.28)***	4.33 (3.74 – 4.92)	7.00 (6.59 – 7.40)***	4.98 (4.42 – 5.55)	7.13 (6.53 – 7.73)***
Past, n = 1,644	4.24 (4.02 – 4.47)	7.22 (6.88 – 7.56)***	3.67 (3.44 – 3.91)	6.76 (6.55 – 6.96)***	4.20 (3.97 – 4.24)	7.09 (6.76 – 7.41)***
Never, n = 2,261	2.01 (1.89 – 2.14)	6.16 (5.61 – 6.71)***	1.65 (1.54 – 1.76)	5.42 (5.17 – 5.68)***	1.97 (1.85 – 2.10)	5.87 (5.39 – 6.35)***
Wald F-test p-value[e]	**< 0.001**	**< 0.001**	**< 0.001**	**< 0.001**	**< 0.001**	**< 0.001**

Abbreviations: CRS = chronic rhinosinusitis; EPOS = European Position Paper on Rhinosinusitis; NSS = nasal and sinus symptoms

*p-value<0.05, **p-value<0.01, ***p-value<0.001; p < 0.05 = statistically significant

[a] Estimates determined by survey-corrected methods and robust standard error estimation; severity determined by use of visual analog scale (0-10), where higher scores indicate more severe NSS

[b] $EPOS_S$ CRS status determined using baseline and fall exacerbation questionnaires: current long-term CRS = EPOS epidemiologic criteria fulfilled at both questionnaires; current recent CRS = current CRS at fall questionnaire, but not at baseline; past CRS = EPOS epidemiologic criteria fulfilled in lifetime, but not during study; never CRS = EPOS epidemiologic criteria never met

[c] AENSS-Med = worse or much worse NSS in past 4 weeks and treated with either oral corticosteroids or antibiotics for worsened symptoms

[d] AENSS-Sx = worse or much worse NSS in past 4 weeks and worsened symptoms lasting 1 week or more

[e] AENSS-Sx-Pur = worse or much worse NSS in past 4 weeks, worsened symptoms lasting 1 week or more, and one of worsened symptoms was green/yellow nasal discharge (mucopurulence)

[f] Wald F-tests were estimated for group comparisons

Table 3.7.4. Figure 2 seasonal prevalence estimates of exacerbated nasal and sinus symptoms, by $EPOS_S$ CRS status and exacerbation definition

$EPOS_S$ CRS status [a]	Season[b]	AENSS-Med[c]	AENSS-Sx[d]	AENSS-Sx-Pur[e]
		Row Percentage[f] (95% Confidence Interval)		
Current long-term, n = 558	Fall	7.77 (4.73 – 12.53)	29.7 (20.8 – 40.6)	10.9 (6.15 – 18.5)
	Winter	20.6 (12.9 – 31.2)	35.1 (26.3 – 45.1)	10.4 (7.05 – 15.0)
	Spring	5.94 (3.28 – 10.5)	33.5 (23.2 – 45.6)	10.8 (6.73 – 16.9)
	Summer	9.15 (5.03 – 16.1)	45.3 (31.4 – 59.9)	11.71 (5.59 – 22.9)
	p-value[g]	**0.02**	0.41	0.99
Current recent, n = 273	Fall	7.63 (3.91 – 14.4)	27.7 (17.2 – 41.4)	6.01 (2.70 – 12.8)
	Winter	7.67 (4.18 – 13.6)	33.2 (22.4 – 46.2)	10.2 (5.96 – 17.0)
	Spring	8.95 (3.10 – 23.2)	31.5 (20.0 – 45.9)	4.83 (2.39 – 9.50)
	Summer	11.4 (3.83 – 29.2)	26.2 (13.6 – 44.6)	5.08 (1.55 – 15.4)
	p-value	0.92	0.71	0.17
Past, n = 1,644	Fall	4.08 (2.49 – 6.62)	16.3 (12.7 – 20.7)	4.99 (3.08 – 7.97)
	Winter	9.29 (6.98 – 12.3)	30.0 (25.0 – 35.5)	13.5 (9.81 – 18.2)
	Spring	6.67 (4.33 – 10.1)	29.0 (23.6 – 35.1)	7.89 (5.05 – 12.1)
	Summer	3.89 (1.40 – 10.3)	21.2 (15.0 – 29.1)	3.91 (2.29 – 6.58)
	p-value	**0.002**	**<0.001**	**<0.001**
Never, n = 2,261	Fall	1.92 (1.13 – 3.23)	8.29 (6.40 – 10.7)	3.40 (2.17 – 5.29)
	Winter	2.67 (1.77 – 4.02)	13.3 (11.0 – 15.9)	4.11 (2.88 – 5.83)
	Spring	3.98 (2.63 – 5.99)	19.6 (16.4 – 23.2)	6.06 (4.17 – 8.73)
	Summer	1.54 (0.71 – 3.27)	7.76 (5.77 – 10.4)	1.29 (0.71 – 2.33)
	p-value	0.08	**< 0.001**	**< 0.001**

Abbreviations: AENSS = acute exacerbation of nasal and sinus symptoms; CRS = chronic rhinosinusitis; EPOS = European Position Paper on Rhinosinusitis; NSS = nasal and sinus symptoms
p-value < 0.05 is significant
[a] $EPOS_S$ CRS status determined using baseline and fall exacerbation questionnaires: current long-term CRS = EPOS epidemiologic criteria fulfilled at both questionnaires; current recent CRS = current CRS at fall questionnaire, but not at baseline; past CRS = EPOS epidemiologic criteria fulfilled in lifetime, but not during study; never CRS = EPOS epidemiologic criteria never met
[b] Season: Autumn = September 22 through December 21; Winter = December 22 through March 21; Spring = March 22 through June 21; Summer = June 22 through September 21
[c] AENSS-Med = worse or much worse NSS in past 4 weeks and treated with either oral corticosteroids or antibiotics for worsened symptoms
[d] AENSS-Sx = worse or much worse NSS in past 4 weeks and worsened symptoms lasting 1 week or more
[e] AENSS-Sx-Pur = worse or much worse NSS in past 4 weeks, worsened symptoms lasting 1 week or more, and one of worsened symptoms was green/yellow nasal discharge (mucopurulence)
[f] Estimates determined by survey-corrected methods and robust standard error estimation
[g] Wald F-tests were estimated for comparing seasons

Table 3.7.5. Overlap of AENSS definitions (row/colum percentages and 95% confidence intervals)[a]

	AENSS-Med[b]	
AENSS-Sx[c]	No	Yes
No	99.4 (98.9 – 99.6) / 86.3 (84.9 – 87.6)	0.6 (0.39 – 1.07) / 13.6 (8.67 – 20.8)
Yes	79.5 (76.3 – 82.3) / 13.7 (12.4 – 15.1)	20.6 (17.7 – 23.7) / 86.4 (79.2 – 91.3)
	AENSS-Med	
AENSS-Sx-Pur[d]	No	Yes
No	97.5 (96.9 – 98.0) / 96.3 (95.6 – 97.0)	2.5 (2.03 – 3.07) / 60.3 (53.1 – 67.0)
Yes	69.2 (62.6 – 75.1) / 3.66 (3.04 – 4.39)	30.8 (25.0 – 37.4) / 39.7 (33.0 – 47.0)
	AENSS-Sx	
AENSS-Sx-Pur	No	Yes
No	87.9 (86.6 – 89.1) / 100	12.1 (10.9 – 13.4) / 69.3 (65.4 – 73.0)
Yes	0 / 0	100 / 30.7 (27.0 – 34.6)

Abbreviations: AENSS = acute exacerbation of nasal and sinus symptoms

[a] Estimates determined by survey-corrected methods and robust standard error estimation

[b] AENSS-Med = worse or much worse NSS in past 4 weeks and treated with either oral corticosteroids or antibiotics for worsened symptoms

[c] AENSS-Sx = worse or much worse NSS in past 4 weeks and worsened symptoms lasting 1 week or more

[d] AENSS-Sx-Pur = worse or much worse NSS in past 4 weeks, worsened symptoms lasting 1 week or more, and one of worsened symptoms was green/yellow nasal discharge (mucopurulence)

Chapter 4: Workplace indirect cost impacts of nasal and sinus symptoms and related conditions

4.0 Cover page

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4.1 Abstract

Objective: Evaluate associations of nasal and sinus and related symptoms, as well as selected health conditions which produce those symptoms, with total lost productive time (LPT) at work in the past two weeks.

Methods: We used a cross-sectional analysis of 2402 currently working subjects. Self-reported physician diagnoses, condition statuses measured with standardized instruments, and symptom-based factor scores from an exploratory factor analysis were used in survey weighted log-binomial regression.

Results: Pain and pressure, nasal blockage and discharge, and asthma and constitutional symptom factor scores as well as self-reported allergic rhinitis were associated with higher total LPT. Individuals who met operationalized criteria for multiple health conditions, especially chronic rhinosinusitis, had the greatest total LPT.

Conclusions: Better management of these symptoms, and awareness of how they impact an individual's ability to perform job-functions in the workplace, could improve overall productivity.

4.2 Introduction

Cost is an important component in determining the overall burden of a disease,[1] often broken-down into two primary sources: direct and indirect. Direct costs include expenditures related to the medical treatment and care received for a condition while indirect costs are commonly characterized by daily life and employment impacts of a condition. In the workplace, indirect costs often include absenteeism (missing work due to health conditions) and presenteeism (reduced productivity and performance at work due to health conditions), which are jointly referred to as total lost productive time (LPT).[2] Acute conditions, like influenza, often have more indirect costs than direct costs,[1,3] whereas chronic conditions, like diabetes, have larger direct costs.[4]

Chronic rhinosinusitis (CRS) is an upper respiratory condition characterized by inflammation of the nasal and paranasal sinuses,[5-7] that is estimated to affect nearly 12% of the adult US population,[7] and incurs $22-$32 billion in total costs yearly.[8,9] The European Position Paper on Rhinosinusitis and Nasal Polyps symptom-based criteria (CRS_S) is commonly used for CRS classification in epidemiologic studies.[5] Individuals with CRS_S have been shown to have severe, persistent, and bothersome symptoms[10] that would be expected to impact workplace productivity. Previous studies have shown CRS to result in increased absenteeism[11-17] and presenteeism[12,15,17,18] with estimates as high as 24.6 and 38.8 days per year, respectively.[18] These studies have focused on individuals in the more severe spectrum of disease with many focused solely on recalcitrant or refractory CRS after surgery.[15,17,18]

To date, no study has evaluated the workplace impacts of CRS across the full spectrum of disease in a general population representative sample. CRS is often comorbid with several conditions (e.g., allergic rhinitis [hay fever], asthma, migraine headache)[19,20] and the nasal and sinus symptoms (NSS) used in CRS_S criteria often occur

from these conditions as well. Further, these conditions have been shown to increase absenteeism,[21-25] presenteeism,[21-25] and total LPT.[26,27] Several of these conditions with overlapping symptoms are diagnosed solely on the basis of symptoms (e.g. migraine headache), while others have additional evidence that can assist diagnosis (e.g., pulmonary function tests, skin allergy testing, sinus CT scan). Treatment for some of these conditions itself can have side effects that themselves impact work. Few prior studies have attempted to disentangle whether aspects of the diagnosis itself, which could capture the impact of treatment side effects, or the specific associated symptoms, were most associated with increased LPT.[12,17]

Given the lack of general population-based epidemiologic studies of NSS due to CRS and related conditions with workplace impacts, the overarching objective of this study was to identify risk factors for LPT in a generalizable, population-based sample. To accomplish this objective, we used electronic health records (EHR) of subjects who had a primary care provider from Geisinger, a healthcare system in over 40 counties in central and northeastern Pennsylvania; these subjects are representative of the general population for the region.[28]

4.3 Materials and methods

4.3.1 Study overview

We performed a cross-sectional analysis using responses to the final questionnaire in a longitudinal study of subjects focused on NSS and CRS, described elsewhere.[7,29] Briefly, we sequentially mailed five self-administered questionnaires from April 2014 through December 2015 to a stratified random sample of primary care patients of Geisinger. Details of items included in questionnaires are described elsewhere.[29] Briefly, the four questionnaires following baseline were used to understand seasonal exacerbations of NSS and were sent in approximately four month intervals. This study was approved by the Institutional Review Board (IRB) of Geisinger, which has an IRB

Authorization Agreement with the Johns Hopkins Bloomberg School of Public Health. Health Insurance and Accountability Act authorization and written informed consent waivers were approved by the IRB.

4.3.2 Sampling method and study population

A description of the sampling method has been previously reported.[7] Electronic health records (EHR) were utilized to categorize individuals into three groups based on International Classification of Disease-9 and Current Procedural Terminology codes for allergic rhinitis, asthma, CRS, nasal polyps, and sinus procedures. We over-sampled individuals with CRS, nasal polyp, allergic rhinitis, and asthma diagnostic codes, as well as racial/ethnic minorities.[7] Of the 23,700 individuals randomly selected to participate in the longitudinal study, 7847 responded to the baseline survey and 4600 responded to the final follow-up questionnaire.

4.3.3 Primary independent variables

We first operationalized definitions and analytic variables for the primary independent variables of interest, including condition statuses and symptoms.

4.3.3.1 *CRS classification*

We used the CRS_S criteria for categorizing individuals with CRS as previously reported.[7,10,29] CRS_S status (referred to as CRS) was determined using self-reported frequency (in the past three months) of the cardinal CRS symptoms (nasal blockage, green or yellow discharge [anterior or posterior], smell loss, and facial pain or pressure) at each questionnaire. These symptoms were self-reported using a five-point Likert scale ("never", "once in a while", "some of the time", "most of the time", and "all of the time"). Symptoms reported at least "most of the time" were considered towards CRS_S criteria. Individuals were assigned into three CRS status groups: "never" (did not meet current CRS_S criteria at any questionnaire), "past" (met criteria at a prior questionnaire but not at the last one), and "current" (met criteria at last one).

4.3.3.2 *Self-reported physician diagnoses and migraine headache status*

Self-reported physician diagnosis of hay fever and asthma were ascertained at baseline. Migraine status was operationalized as a binary indicator and determined using standardized and validated methods.[29,30]

4.3.3.3 *Symptom factor scores*

Factor scores were estimated from five factors using factor weights and methods previously described.[31] Briefly, three EFA models were performed using 3535 subjects with responses to baseline, six month, and 16-month (final) questionnaires. Indicators included in the EFA were 37 self-reported symptoms in the categories of nasal and sinus; ear and eye; asthma; constitutional symptoms (i.e., fever, headache, fatigue); and allergy symptoms. Five factors were identified by the EFA models as pain and pressure; blockage and discharge; asthma and constitutional; smell loss; and ear and eye symptoms. Factor weights from the 16-month questionnaire EFA were used to estimate factor scores as previously reported.[31] Larger scores indicated greater reporting of symptoms relevant to the specific factor and were standardized by z-transformation to allow for comparisons of factors.

4.3.4 Dependent variables: absenteeism, presenteeism, and lost productive time

Questions from the Work and Health Interview[32] were only included in the 16-month questionnaire, using a two-week recall period. Subjects were instructed to complete the work-related questions only if they were currently working. Questions ascertained the average number of days worked per week and hours worked per day, which were then combined to calculate the average total hours worked in the prior two weeks. NSS-specific absenteeism was operationalized from two questions: “How many workdays did you miss in the past two weeks because you were not feeling well?” and “How many of the workdays in the past two weeks were missed due to nasal and sinus symptoms?” We estimated lost productivity while at work (presenteeism) due to NSS in two

components. We first estimated presenteeism days with responses to two questions: “On how many days in the past two weeks did you go to work when not feeling well?” and “On the days in the past two weeks you were not feeling well at work how many were due to your nasal and sinus symptoms?” We then estimated an “impact index” as workplace ability and function while having NSS using responses to five Likert scale questions (Supplemental material **Table 4.7.1**). Each of the five questions were scored from 0 to 1 (1 = all of the time; 0.75 = most of the time; 0.50 = about half of the time; 0.25 = some of the time; 0 = none of the time) and the final index score was the mean of the five questions. Finally, the product of presenteeism days and the impact index provided the total number of NSS-specific presenteeism days. Both absenteeism and presenteeism were converted from days to hours using estimated hours worked per two-week period. Lastly, total LPT was estimated by adding NSS-specific absenteeism and presenteeism for each subject.

4.3.5 Statistical analyses

The primary goals of the analysis were to evaluate whether: 1) symptom-based factor scores from an exploratory factor analysis (EFA)[31] of a range of symptoms from several related conditions (i.e., asthma, CRS, hay fever, migraine headache) were more strongly associated with total LPT than were operationalized or self-reported physician diagnoses of these conditions; and 2) estimate and compare average total LPT within subgroups based on CRS and other health conditions to characterize subgroups with higher average total LPT.

Of the 4600 subjects who responded to the final questionnaire, 2402 had classifiable CRS status and reported currently working and were therefore included in the analysis. Relations between variables as well as distributions were assessed and missing data on selected covariates were multiply imputed as done previously.[29] For adjusted estimates of total LPT, three log-binomial regression models were assessed: model 1 evaluated

symptom factors; model 2 evaluated condition statuses (e.g. physician-reported hay fever); and model 3 (fully-adjusted) evaluated symptoms and conditions. The outcome in these models was a proportion defined by: the number of work-hours attributed to LPT (numerator) over the average total number of hours worked (denominator), in a two week period.

Potential covariates were selected from prior studies and *a priori* theory and included age (years, centered and scaled per five-years), sex, race/ethnicity (white vs. non-white), receipt of Medical Assistance (a surrogate for family socioeconomic status),[33] body mass index (BMI, kg/m^2), Charlson comorbidity index (centered),[34] smoking status (never, former, current), and education (high school education or less, some college, four or more years of college). Non-linearity in continuous covariates was assessed, resulting in a cubic function for pain and pressure.

To better understand associations observed in the regression models, we estimated LPT over a range of factor score values (**Figure 4.4.2.1**) and in subgroups based on CRS and health conditions using average adjusted predictions (i.e. predictive margins[35]) derived from the fully-adjusted model (**Figure 4.4.2.2**). Hereafter, we refer to these values as average expected total LPT (AET-LPT). While effect estimates from regression models are useful in understanding adjusted relations of covariates with the outcome, this latter approach provides tangible estimates of the expected outcome for, as examples, specific subgroups of people or for different values of specified covariates.

Models were weighted using methods previously described[29] and included use of sampling[7,10] and inverse-probability of censoring weights (IPCW).[29] As done previously,[7,10,29] full weights were used in estimation of descriptive statistics whereas truncated weights were used in regression modeling. Adequacy of model fit was assessed by inspecting residuals, influence, and leverage, with one observation

ultimately removed from final models. Models with and without this observation were substantively comparable, yet non-linearity of pain and pressure factor score was attenuated when the observation was included. Statistical analyses were performed using STATA v15.1 (StataCorp, College Station, TX, USA) and R v3.4.1 (R Foundation for Statistical Computing, Vienna, Austria; www.r-project.org) software packages.

4.3.6 Sensitivity analyses

We did not include CRS status in model 3 since questions used to operationalize CRS_S were also included in the factors, thereby inducing a linear dependency. However, we did test an additional model in which we included CRS status as a covariate. We also assessed sensitivity of observed effect estimates (for model 3) to sampling weights by comparing estimates from unweighted, truncated, and fully weighted models.

4.4 Results

4.4.1 Description of study population

Of the 2402 working subjects, a total of 134, 775, and 790 subjects had any hours of absenteeism, presenteeism, and total LPT in the prior two weeks, respectively. The mean (standard error) absenteeism, presenteeism, and total LPT in the past two weeks was 0.40 (0.10), 1.45 (0.17), and 1.86 (0.21) hours, respectively. Compared to subjects included in the study, excluded subjects tended to be older, less healthy (i.e. larger Charlson comorbidity index), and more likely to receive Medical Assistance (Supplemental material **Table 4.7.2**).

Population-estimated (survey weighted) descriptive information for the study sample showed persons with LPT were younger, more likely to be women, had more comorbidities, and were more likely to have past or current CRS (**Table 4.4.1.1**). Average factor scores were estimated in the source population, both overall and in CRS and health condition subgroups (i.e., migraine headache, hay fever, asthma, and combinations [Supplemental material **Figure 4.7.1**]).

Table 4.4.1.1. Population-estimated characteristics based on study sample (n = 2402)

Selected variables	Means (95% confidence intervals)/medians (IQR)[a]		
	No LPT (n = 1612)[b]	**LPT > 0 (n = 790)**	**p-value**
Hours worked per day; mean	8.33 (8.12 – 8.54)	8.52 (8.24 – 8.80)	0.31
Days worked per 2-week period; mean	9.68 (9.49 – 9.87)	10.2 (9.91 – 10.5)	**0.003**
Age (in years); mean	48.4 (47.0 – 49.8)	43.9 (41.7 – 46.0)	**0.001**
Body mass index (BMI; kg/m^2); mean	29.4 (28.7 – 30.0)	29.0 (27.9 – 30.2)	0.62
Charlson comorbidity index; mean	0.79 (0.72 – 0.86)	1.16 (0.97 – 1.33)	**0.001**
Blockage and discharge; median (IQR)	-0.77 (0.91)	0.18 (1.17)	**< 0.001**
Pain and pressure; median (IQR)	-0.82 (0.55)	0.15 (1.58)	**< 0.001**
Asthma and constitutional; median (IQR)	-0.75 (-0.71)	0.16 (1.31)	**< 0.001**
Smell loss; median (IQR)	-0.77 (0)	0.24 (2.19)	**< 0.001**
Ear and eye; median (IQR)	-0.71 (1.07)	0.22 (1.36)	**< 0.001**
	Column percentages (95% confidence intervals)		
Sex (female), n = 1496	59.7 (55.0 – 64.4)	75.8 (69.1 – 82.4)	**< 0.001**
Race/ethnicity (non-white), n = 157	3.73 (3.29 – 4.17)	5.59 (3.79 – 7.40)	0.09
Medical Assistance (ever received)[c], n = 137	5.70 (3.09 – 8.32)	10.3 (5.43 – 15.1)	0.10
CRS_S status (16-month)[d]			
Never, n = 1034	74.7 (70.9 – 78.4)	45.4 (37.2 – 53.6)	**< 0.001**
Past, n = 915	19.5 (16.1 – 22.8)	32.9 (25.7 – 40.0)	**0.001**
Current, n = 453	5.88 (3.89 – 7.87)	21.7 (15.9 – 27.5)	**< 0.001**
Physician diagnosed asthma, n = 573	8.82 (6.82 – 10.8)	23.6 (17.4 – 29.7)	**< 0.001**
Physician diagnosed hay fever, n = 1169	26.2 (22.4 – 30.0)	54.4 (46.2 – 62.6)	**< 0.001**
Migraine headache status, n = 523	11.2 (8.06 – 14.3)	36.0 (28.2 – 43.8)	**< 0.001**

Abbreviations: CRS = chronic rhinosinusitis; EHR = electronic health record; CRS_S = symptoms that meet European Position Paper on Rhinosinusitis definition for CRS symptoms; LPT= lost productive time; NSS = nasal and sinus symptoms

[a] Estimates derived using survey weighted methods; p-values based on F-ratios, except factor scores, which are based on Mann-Whitney-Wilcoxon U-test

[b] LPT estimated using the sum of self-reported days missed and present while ill (in which work productivity was affected) due to NSS

[c] Medical Assistance is determined from the EHR and is a proxy for family socioeconomic status

[d] CRS status determined using self-reported symptoms relevant to CRS_S at all observed time-points; never CRS = never met CRS_S criteria over follow-up; past CRS = met CRS_S criteria at some point in lifetime or over follow-up, but did not meet criteria at time of 16-month follow-up; current CRS = met CRS_S criteria at time of 16-month follow-up

4.4.2 Adjusted estimates of workplace impacts

In an adjusted model with symptom factor scores, three factors were associated with total LPT: pain and pressure, blockage and discharge, and asthma and constitutional (**model 1**, **Table 4.4.2.1**). In the next model, factor scores were removed and condition status for various health conditions were added; in this model, migraine, physician-diagnosed hay fever, and past and current CRS were associated with increased hours of total LPT (**model 2**, **Table 4.4.2.1**). In the fully-adjusted model, factor scores and health condition status were included together; pain and pressure, blockage and discharge, and asthma and constitutional factors, as well as hay fever, remained associated with total LPT (**model 3**, **Table 4.4.2.1**). Generally, estimates and inferences were substantively unchanged when different sampling weights were used (or omitted) (Supplemental material **Table 4.7.3**) or when CRS status was added to model 3 (Supplemental material **Table 4.7.4**).

Table 4.4.2.1. Adjusted log-binomial regression models of total lost productive time (in hours) in two weeks, by symptom factor scores (model 1), selected conditions (model 2), and both (model 3), estimated in the source population[a]

Covariates	Exponentiated β-coefficients[a] (95% confidence interval)		
	Model 1	**Model 2**	**Model 3[b]**
Pain & pressure factor score (FS)[c]			
Linear term	3.38 (2.42 – 4.71)***		3.31 (2.37 – 4.61)***
Squared term[d]	0.47 (0.31 – 0.71)***		0.48 (0.32 – 0.73)***
Cubic term[d]	1.16 (1.02 – 1.32)*		1.15 (1.02 – 1.31)*
Blockage & discharge FS	1.21 (1.01 – 1.45)*		1.21 (1.02 – 1.43)*
Asthma & constitutional FS	1.31 (1.16 – 1.50)***		1.30 (1.14 – 1.48)***
Smell loss FS	0.92 (0.80 – 1.06)		0.90 (0.78 – 1.04)
Ear & eye FS	1.08 (0.91 – 1.28)		1.05 (0.89 – 1.24)
Migraine status (Ref: no)		1.83 (1.31 – 2.55)***	1.24 (0.94 – 1.64)
Physician diagnosed hay fever (Ref: no)		1.61 (1.19 – 2.19)*	1.30 (1.00 – 1.70)*
Physician diagnosed asthma (Ref: no)		1.22 (0.87 – 1.72)	1.20 (0.88 – 1.63)
CRS_S status (Ref: never)[e]			
Past		1.62 (1.10 – 2.38)*	
Current		4.24 (2.85 – 6.29)***	

p-value: < 0.001***, 0.01**, < 0.05*
Abbreviations: CRS = chronic rhinosinusitis; EHR = electronic health record; CRS_S = symptoms that meet European Position Paper on Rhinosinusitis definition for CRS symptoms; LPT= lost productive time; NSS = nasal and sinus symptoms
[a] Estimates derived using survey weighted methods; outcome is a proportion represented by total LPT as the numerator and average total hours worked in a two-week period as the denominator; all models additionally adjusted for: age (centered; scaled by five years), sex, race/ethnicity, Medical Assistance, body mass index (centered), Charlson comorbidity index (centered), smoking status, and education
[b] To avoid linear dependency between current CRS status and the symptom factor scores, CRS_S status was not retained in the final version of model 3 in which all other estimates are based on; estimates for CRS status are only derived from model 2
[c] Factor scores were standardized (*z*-transformed) with units of SDs; entered model as continuous variables
[d] Allowed for non-linearity in association
[e] CRS status determined using self-reported symptoms relevant to CRS_S at all observed time-points; never CRS = never met CRS_S criteria over follow-up; past CRS = met CRS_S criteria at some point in lifetime or over follow-up, but did not meet criteria at time of 16-month follow-up; current CRS = met CRS_S criteria at time of 16-month follow-up

We further evaluated associations of each factor with total LPT by estimating AET-LPT using score values within ± 2 standard deviations, controlling for covariates (**model 3, Table 4.4.2.1** and **Figures 4.4.2.1A-E**). AET-LPT for a one standard deviation increase from the mean pain and pressure factor score would be 4.19 (95% CI: 3.25, 5.13) hours, while a decrease would be 0.29 (95% CI: 0.08, 0.49) hours (**Figure 4.4.2.1A**). Similarly, AET-LPT for a blockage and discharge factor score one standard deviation above or below the mean would be 2.76 (95% CI: 2.01, 3.52) and 1.90 (95% CI: 1.38, 2.42) hours, respectively (**Figure 4.4.2.1B**). AET-LPT for a one standard deviation increase from the mean asthma and constitutional factor score would be 2.98 (95% CI: 2.24, 3.73) hours, while a decrease would be 1.76 (95% CI: 1.33, 2.19) hours (**Figure 4.4.2.1C**). Using the sum of all factor scores as an aggregate measure of all NSS and related symptoms, AET-LPT among subgroups with a score of 0, 5, or 10 would be 2.29 (95% CI: 1.81, 2.78), 6.25 (95% CI: 5.00, 7.50), and 9.20 (95% CI: 6.24, 12.2) hours, respectively (**Figure 4.4.2.1F**).

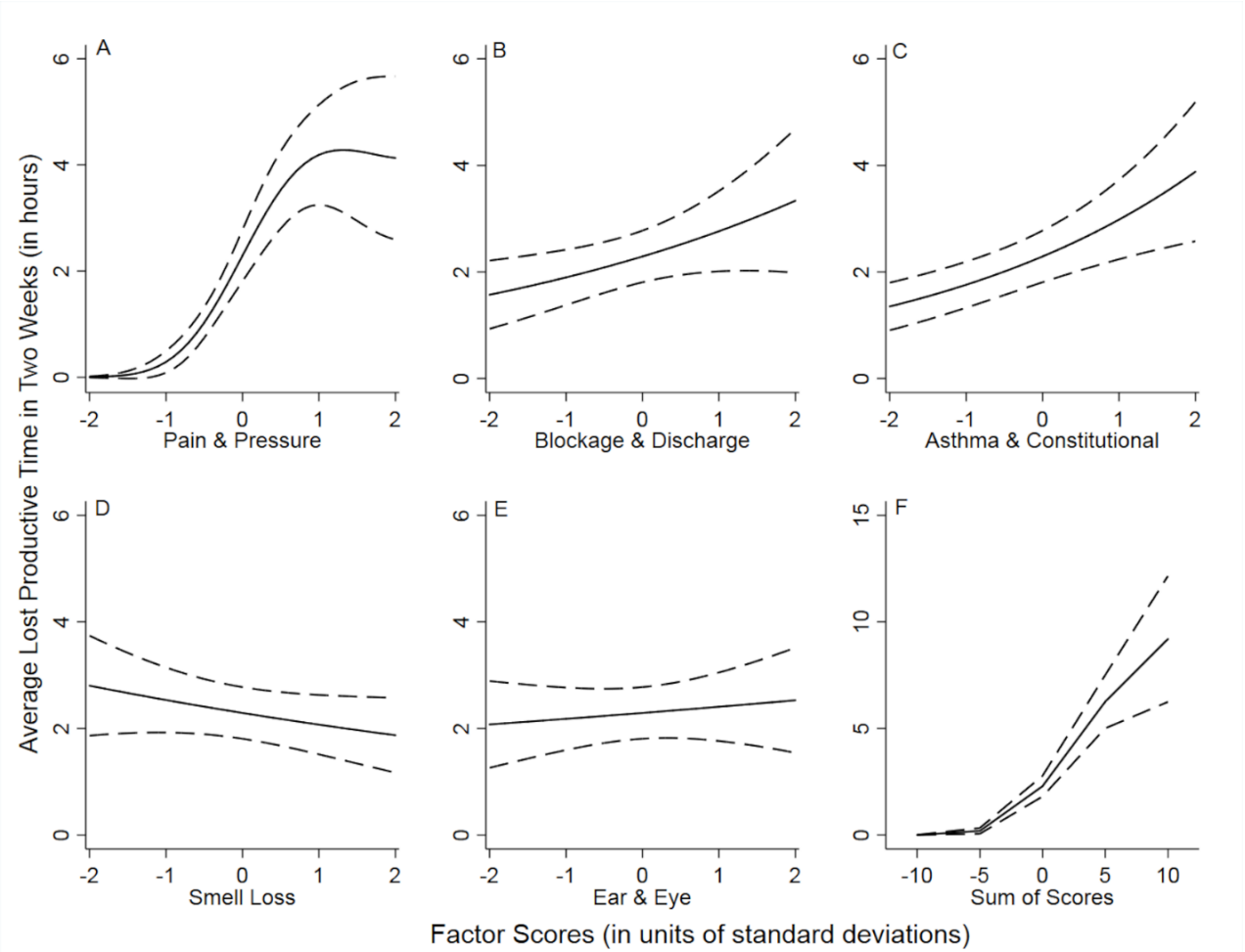

Figure 4.4.2.1. Adjusted average total lost productive time (in hours) in two weeks, by standardized factor scores and sum of factor scores, estimated in the source population. LPT estimates are presented across ± 2 standard deviations for each of five symptom factors: (A) pain and pressure; (B) blockage and discharge; (C) asthma and constitutional; (D) smell loss; (E) ear and eye; and (F) the sum of the five factor scores.

Finally, to understand how associations with symptoms and LPT are represented in subgroups of individuals with these symptoms, we estimated AET-LPT within subgroups based on CRS and health conditions, using the fully-adjusted model (**Figure 4.4.2.2**).

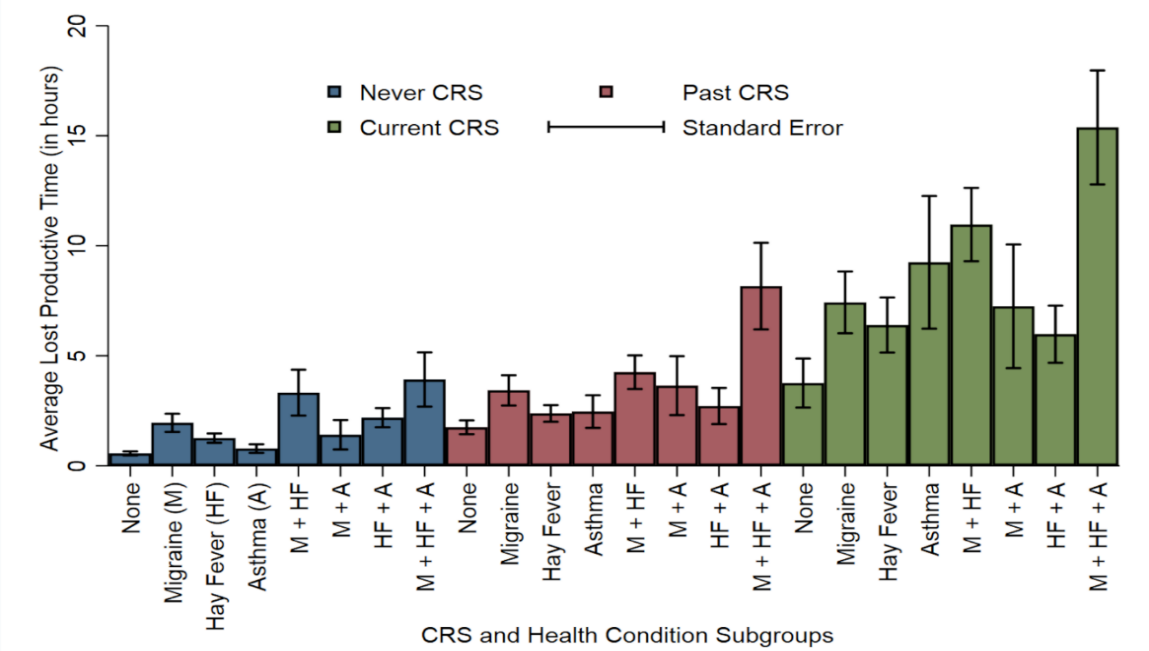

Figure 4.4.2.2 Adjusted average total lost productive time (in hours) in two weeks, by CRS_S and health condition subgroups, estimated in the source population. Estimates based on fully-adjusted model (model 3) associations.

Overall, the current CRS subgroup would be expected to have the most AET-LPT, 7.47 hours (95% CI: 6.11, 8.82) in two weeks. Current CRS subgroups with comorbid asthma, hay fever, or migraine would have an AET-LPT of 9.25 (95% CI: 3.34, 15.2), 6.40 (95% CI: 3.95, 8.85), and 7.42 (95% CI: 4.67, 10.2) hours, respectively. Lastly, the current CRS subgroup with all three comorbidities would have an AET-LPT of 15.4 (95% CI: 10.3, 20.5) hours (**Figure 4.4.2.2**).

4.5 Discussion

In this first general population-based study of the workplace impacts of nasal, sinus, and related symptoms due to CRS and comorbid conditions, several findings were notable. We identified three symptom domains using factor scores that were associated with total LPT, specifically pain and pressure, blockage and discharge, and asthma and

constitutional, with the strongest association for pain and pressure. Before inclusion of these factor scores, past or current CRS, hay fever, and migraine were each associated with total LPT but only hay fever was associated with total LPT when factor scores were included.

We attempted to determine which aspect of a condition was the key determinant of workplace impact by including both symptom factors and condition indicators in the same model. While condition status also encompasses symptoms (as they are generally the basis for diagnosis) it further includes willingness to seek medical care, disease control, medical or surgical treatments (which may affect reported symptoms), and side effects of treatments. By including both measures into a single model, we attempted to disentangle the workplace impacts of symptoms from the other aspects of the studied health conditions. Our results suggest that symptoms are more important than other features of these health conditions, with the symptoms of pain and pressure having a strong association with total LPT.

The finding with the pain and pressure factor is consistent with that of a prior study of CRS and LPT in a tertiary care sample, in which facial pain was found to be highly correlated with workplace presenteeism and total LPT, even with adjustment for total sino-nasal outcomes test (SNOT)-22 scores (which includes nasal and sinus, fatigue, and allergy symptoms) and confounding variables.[12] The results of both studies suggest that facial pain is associated with LPT even after accounting for differences in co-occurring symptoms. Our observed association between nasal blockage and discharge and total LPT is also supported by a study of SNOT-22 domains and indirect costs among individuals with refractory CRS, where increases in monetary costs were associated with a one standard deviation increase in extra-nasal rhinologic symptoms (e.g. nasal discharge).[17] Asthma, particularly poorly controlled, has reportedly been

associated with workplace impacts,[23,24] and our association of the asthma and constitutional factor with total LPT is consistent with prior literature. Our lack of an association for the smell loss factor score is also consistent with a recent study of olfactory dysfunction and total LPT among individuals with recalcitrant CRS using an objective measure of smell loss.[36]

Current CRS was associated with more total LPT than never or past CRS. Symptoms of blockage and discharge as well as facial pain and pressure are used in CRS_S criteria for current CRS classification. Given this dependence on these symptoms for classification, it is perhaps unsurprising that current CRS was associated with total LPT in a model which only included conditions, since several studies of mainly tertiary care populations have shown CRS to influence workplace productivity among persons with it.[12,15,18] It is important to note the association of current CRS was attenuated when symptom factor scores were included in the same model. While this could be due to modest collinearity, it may also imply that it was the symptom-based components of current CRS classification which drove its association with total LPT, as opposed to aspects of medical and/or surgical treatments.

Hay fever was the only condition to remain associated with LPT in the fully-adjusted model. We speculate that only individuals with the most severe hay fever symptoms would seek medical care and thus have a physician diagnosis; however, the observation could also be due to side effects of some allergy medications, which have been associated with LPT.[37]

Estimates of total LPT share similarities with previous findings. A prior study of total LPT among migraineurs found a range of 0.98 – 4.07 and 0.83 – 4.95 hours of total LPT per week among white females and males, respectively, ages 45-54 years.[27] Our study estimates are comparable. A pain and pressure symptom factor score one standard

deviation above average predicted 4.19 hours of total LPT per two weeks (~2.10 hours per week), while migraineurs with no history of CRS and other comorbidities were predicted to have 1.95 hours of total LPT per two weeks (~0.98 hours per week). Our study also found results differing from prior studies. For example, a study of CRS estimated an average workplace impact of 63.4 days of total LPT per year (507.2 hours assuming 8-hr work periods) among persons with CRS.[18] The discrepancy is likely because the latter study was only of persons with refractory CRS selected from tertiary-referral centers, so represents the most extreme end of the disease spectrum.

Our study had several strengths. This is the first study, to our knowledge, to estimate and compare the workplace impacts of several conditions in a general population-based sample including CRS subjects with the full spectrum of disease, not only those cared for in tertiary care referral facilities. We examined symptom-based factors and evaluated their associations with total LPT with and without inclusion of specific health conditions in the models, disentangling the role of symptoms and other features of the health conditions on total LPT.

This study also had limitations. We did not have occupational information (e.g. job title) for the subjects included in this study. We were thus unable to incorporate job type in analyses. We were also unable to account for differences in workplace culture and workplace policies (e.g., sick time, personal time off without having to provide medical documentation, light duty) that could differentially influence how symptomatic conditions could be translated into absence time and presenteeism. Finally, we studied self-reported physician diagnoses, self-reported symptoms, and conditions based on standardized screening instruments, but were not able to include objective evidence of inflammation in our CRS definition.

In this first population-based study of NSS and other symptoms from CRS and related health conditions, we found that rigorously estimated factor scores in the domains of pain and pressure, nasal blockage and discharge, and asthma and constitutional symptoms were associated with increased total LPT. Awareness for how these symptoms may impact a person's ability to perform necessary job functions, as well as better management of symptoms, may ultimately lead to improved workplace productivity.

4.6 References

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Table 4.7.1. Five Likert scale questions used to create nasal and sinus symptom (NSS) impact index

Question #	Question text
Q1	On the day(s) you went to work with nasal and sinus symptoms, on average, how much of the time did you just do no work when you were supposed to be working?
Q2	On the day(s) you went to work with nasal and sinus symptoms, how much of the time did you spend doing a job over because you made a mistake or your supervisor told you to do a job over?
Q3	On the day(s) you went to work with nasal and sinus symptoms, how much of the time did you find it difficult to concentrate on what you needed to do?
Q4	On the day(s) you went to work with nasal and sinus symptoms, how much of the time did you work more slowly or take longer to complete tasks than usual or expected?
Q5	On the day(s) you went to work with nasal and sinus symptoms, how much of the time were you very tired, fell asleep at work or just felt too exhausted to do your work?

Table 4.7.2. Comparison of subjects included and excluded from study (at 16-month follow up)

Selected variables	Means (95% confidence intervals)[a]		
	Not in study (n = 2198)	**In study (n = 2402)**	**p-value**
Age (in years)	65.4 (64.8 – 65.9)	50.6 (50.1 – 51.1)	**< 0.001**
Body mass index (BMI; kg/m^2)	30.1 (29.9 – 30.4)	30.0 (29.7 – 30.3)	0.47
Charlson comorbidity index	2.18 (2.11 – 2.25)	1.55 (1.49 – 1.60)	**< 0.001**
Column Percentages (95% confidence intervals)			
Sex (female), n = 2854	61.8 (59.8 – 63.8)	62.3 (60.3 – 64.2)	0.73
Race/ethnicity (non-white), n = 314	7.14 (6.07 – 8.22)	6.53 (5.55 – 7.52)	0.42
Medical Assistance (ever received)[b], n = 354	9.87 (8.63 – 11.1)	5.70 (4.78 – 6.63)	**< 0.001**

Abbreviations: CRS = chronic rhinosinusitis; EHR = electronic health record; CRS_S = symptoms that meet European Position Paper on Rhinosinusitis definition for CRS symptoms; LPT= lost productive time; NSS = nasal and sinus symptoms

[a] P-values based on F-ratios

[b] Medical Assistance is determined from the EHR and is a proxy for family socioeconomic status

Table 4.7.3. Effect estimates for unweighted, truncated weighted, and fully weighted versions of model 3

Covariates	Exponentiated β-coefficients[a] (95% confidence interval)		
	Unweighted	**Truncated**	**Full**
Pain & pressure FS[b]			
Linear term	3.03 (2.39 – 3.84)***	3.31 (2.37 – 4.61)***	2.49 (1.54 – 4.03)***
Squared term[c]	0.51 (0.38 – 0.67)***	0.48 (0.32 – 0.73)***	0.66 (0.34 – 1.27)
Cubic term[c]	1.16 (1.06 – 1.26)**	1.15 (1.02 – 1.31)*	1.05 (0.86 – 1.28)
Blockage & discharge FS	1.12 (0.97 – 1.28)	1.21 (1.02 – 1.43)*	1.20 (0.97 – 1.49)
Asthma & constitutional FS	1.24 (1.12 – 1.38)***	1.30 (1.14 – 1.48)***	1.34 (1.15 – 1.55)***
Smell loss FS	1.02 (0.93 -1.12)	0.90 (0.78 – 1.04)	0.90 (0.75 – 1.07)
Ear & eye FS	1.09 (0.97 – 1.23)	1.05 (0.89 – 1.24)	1.12 (0.89 – 1.41)
Migraine status (Ref: no)	1.22 (1.01 – 1.47)*	1.24 (0.94 – 1.64)	1.48 (1.03 – 2.11)*
Physician diagnosed hay fever (Ref: no)	1.08 (0.89 – 1.32)	1.30 (1.00 – 1.70)*	1.53 (1.07 – 2.19)*
Physician diagnosed asthma (Ref: no)	0.82 (0.64 – 1.07)	1.20 (0.88 – 1.63)	1.13 (0.78 – 1.65)

Abbreviations: CRS = chronic rhinosinusitis; EHR = electronic health record; CRS_S = symptoms that meet European Position Paper on Rhinosinusitis definition for CRS symptoms; FS = factor score; LPT= lost productive time; NSS = nasal and sinus symptoms

[a] Estimates derived using survey weighted methods; outcome is a proportion represented by total LPT as the numerator and average total hours worked in a two-week period as the denominator; all models additionally adjusted for: age (centered; scaled by five years), sex, race/ethnicity, Medical Assistance, body mass index (centered), Charlson comorbidity index (centered), smoking status, and education

[b] Factor scores were standardized (*z*-transformed) with units of SDs; entered model as continuous variables

[c] Allowed for non-linearity in association

Table 4.7.4. Effect estimates for model 3 which included CRS_S status

Covariates	Exponentiated β-coefficients[a] (95% confidence interval) Model 3
Pain & pressure FS[b]	
Linear term	3.42 (2.48 – 4.72)***
Squared term[c]	0.46 (0.31 – 0.70)***
Cubic term[c]	1.16 (1.02 – 1.31)*
Blockage & discharge FS	1.19 (0.98 – 1.45)
Asthma & constitutional FS	1.29 (1.14 – 1.47)***
Smell loss FS	0.90 (0.78 – 1.04)
Ear & eye FS	1.05 (0.89 – 1.23)
Migraine status (Ref: no)	1.25 (0.94 – 1.67)
Physician diagnosed hay fever (Ref: no)	1.30 (1.00 – 1.69)
Physician diagnosed asthma (Ref: no)	1.22 (0.90 – 1.65)
CRS_S status (Ref: never)[d]	
Past	0.82 (0.58 – 1.16)
Current	1.05 (0.67 – 1.64)

p-value: < 0.001***, 0.01**, < 0.05*

Abbreviations: CRS = chronic rhinosinusitis; EHR = electronic health record; CRS_S = symptoms that meet European Position Paper on Rhinosinusitis definition for CRS symptoms; FS = factor score; LPT= lost productive time; NSS = nasal and sinus symptoms

[a] Estimates derived using survey weighted methods; outcome is a proportion represented by total LPT as the numerator and average total hours worked in a two-week period as the denominator; all models additionally adjusted for: age (centered; scaled by five years), sex, race/ethnicity, Medical Assistance, body mass index (centered), Charlson comorbidity index (centered), smoking status, and education

[b] Factor scores were standardized (*z*-transformed) with units of SDs; entered model as continuous variables

[c] Allowed for non-linearity in association

[d] CRS status determined using self-reported symptoms relevant to CRS_S at all observed time-points; never CRS = never met CRS_S criteria over follow-up; past CRS = met CRS_S criteria at some point in lifetime or over follow-up, but did not meet criteria at time of 16-month follow-up; current CRS = met CRS_S criteria at time of 16-month follow-up

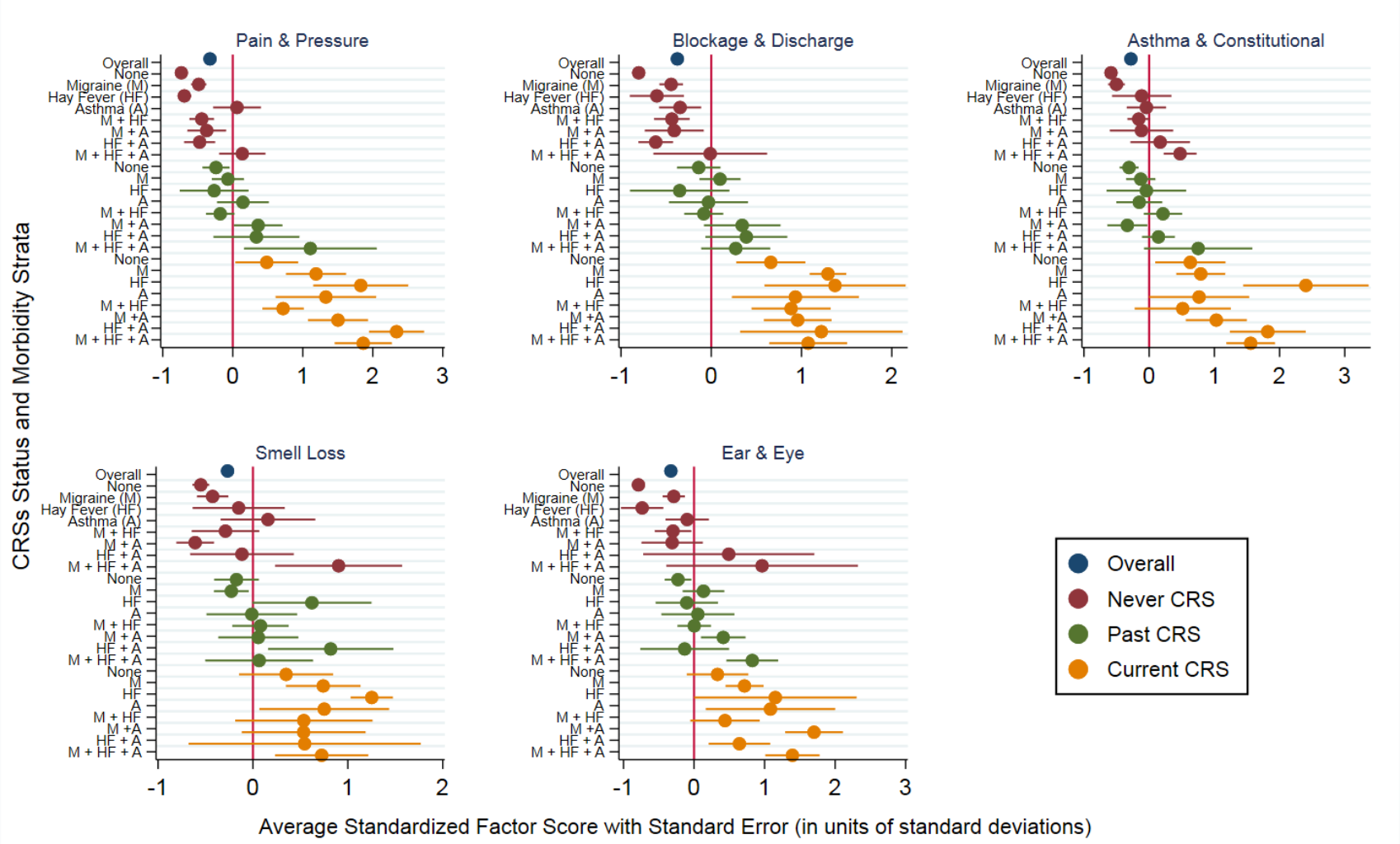

Figure 4.7.1. Average standardized factor scores from weighted analysis, overall and by CRS_S status and morbidity strata

Chapter 5: A new approach to categorization of radiologic inflammation in chronic rhinosinusitis

5.0 Cover page

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5.1 Abstract

Background: Chronic rhinosinusitis (CRS) is a prevalent condition. Clinical diagnosis requires subjective evidence (i.e. symptoms) and objective evidence of inflammation (e.g. sinus computed tomography [CT]). Few studies have assessed differences in common CT scoring approaches for CRS, the Lund-Mackay (LM) system and its modified version (mLM); none in a general population sample.

Objectives: To answer the following: (1) Did mLM improve upon LM? (2) Should nasal cavity opacification be included as part of scores? (3) How should location-specific scores be utilized? (4) If location-specific scores are summed, what should be the cutoff? (5), Are associations of opacification with symptoms observed when using different approaches to measurement?

Methods: We used sinus CT scans scored using LM and mLM from 526 subjects selected from a larger CRS study. Exploratory factor analysis (EFA) assessed equivalence of mLM and LM. Latent class analysis (LCA) identified subgroups of sinus opacification patterns. Clinical relevance of latent classes was assessed by investigating associations with nasal and sinus symptoms (NSS) using least absolute deviation and multivariate ordered probit regression analyses.

Results: EFA suggested all sinuses measured the same construct, with no differences between LM and mLM, or after addition of nasal cavity opacification. LCA identified three subgroups of opacification: no/mild, localized, and diffuse. An LM cutoff of 3 has similar performance to the currently used 4. Diffuse opacification was associated with nasal blockage, smell loss, and overall NSS burden.

Conclusions: Latent classes of sinus opacification may have clinical relevance improving measurement of objective evidence in studies of CRS and sinus diseases.

5.2 Introduction

Chronic rhinosinusitis (CRS) is a prevalent condition of the paranasal sinuses.[1] Clinical diagnosis of CRS, suggested by American,[2] European,[1] and international[3] consensus groups, requires two components: 1) objective evidence of sinus inflammation by imaging (e.g. computed tomography [CT] scan) or nasal endoscopy, and 2) subjective evidence of self-reported nasal and sinus (NSS) symptoms. Considering the difficulty and cost associated with obtaining objective evidence of inflammation, EPOS has also proposed a symptom-based CRS definition (CRS_S) to be used in epidemiologic research.[1]

The Lund-Mackay (LM)[4] scoring approach is recommended for CRS[5] and measures opacification in three categories (none, partial, total) in five sinuses (maxillary, anterior and posterior ethmoids, frontal, and sphenoid) as well as the osteomeatal complex (OMC, none or total), with individual scores summed to a total of 0-24. A previous study of tertiary care patients with indications requiring sinus CT scans suggested a total score of LM < 4 be used as the cutoff for determining "normal" sinus opacification.[6] The modified LM (mLM)[7,8] is a variant of LM with finer gradation in sinus opacification (five categories) allowing for a total score of 0-44. Neither approach includes nasal cavity opacification as part of the total score, despite the fact that nasal polyposis, usually detected through endoscopic examination of the nasal cavity, causes nasal cavity opacification, and characterizes one phenotype of CRS (CRS with nasal polyps [CRSwNP]).[1]

It has been well-documented that objective and subjective evidence of CRS correlate poorly;[5,9-11] however, there are many potential reasons for the observed inconsistencies. NSS are common to several conditions e.g., acute rhinosinusitis (ARS), allergic rhinitis, migraine headache; therefore, individuals with these morbidities often meet criteria for

CRS$_S$ while having no objective evidence of sinus inflammation. Further, symptom scoring approaches like CRS$_S$ consider NSS to be largely interchangeable; however, a recent study of NSS has shown the four symptom groups used in CRS$_S$ (nasal blockage/congestion/obstruction; anterior/posterior nasal discharge; smell loss; and facial pain/pressure), identify separate constructs, not one, which would be expected if they all represent the same underlying process or pathogenesis.[12] Additionally, sinus opacification in the general population has not been studied so there have not been rigorous approaches to measurement across the broad spectrum of disease. Considering causation, inflammation causes manifestation of symptoms, not vice versa. Given the above, it is not surprising that NSS cannot be used to identify those likely to have sinus opacification. Given the widespread use of LM for diagnosis of sinus disease, this study had five primary objectives: 1) evaluate two common scoring approaches, mLM and LM, to determine whether mLM had better measurement properties compared to LM; 2) given that nasal polyps eventually extend to the nasal cavity, determine whether addition of nasal cavity opacification impacted scoring approaches; 3) assess whether sinus scores should be summed into one index, as current scoring proposes, or whether other approaches to measurement provide additional information; 4) if sinus locations are to be summed, determine if the current cutoff of LM ≥ 4 is suggested based on a general population sample; and 5) based on findings 1-4, determine whether new approaches to measurement of radiologic inflammation are associated with NSS.

5.3 Materials and methods

5.3.1 Study overview and participant selection

Low-dose radiation sinus CT scans were completed on 646 subjects selected from a larger longitudinal study of CRS epidemiology. Details of the longitudinal study have been published elsewhere.[13,14] Briefly, in 2014, primary care patients at least 18 years of age were selected (n = 23,700) from the electronic health record (EHR) of Geisinger, a

health system in Pennsylvania and New Jersey in over 40 counties and whose primary care population is representative of the general population,[15] to participate in the longitudinal study. Individuals who responded to the baseline questionnaire (n = 7847) were additionally mailed four seasonal follow-up questionnaires over the course of 16-months.

We used a stratified-random sampling approach to over-sample individuals with NSS as well as racial/ethnic minorities. NSS questionnaires were sent to subjects prior to their scheduled CT visit. Subjects who were pregnant were excluded and subjects reporting a cold or upper respiratory infection in the past 30 days were asked to postpone their CT visit. Of the 3269 subjects invited to participate in the CT study, 646 completed a sinus CT.

This study was approved by Geisinger's Radiation Safety Committee and Institutional Review Board (IRB), which has an IRB Authorization Agreement with the Johns Hopkins Bloomberg School of Public Health. Health Insurance Portability and Accountability Act authorization was approved and written informed consent was received from all participants.

5.3.2 CT imaging, staging, and scoring

Low-dose radiation, non-contrast sinus CT scans (coronal 3mm slices) were completed for all study subjects. CT images were de-identified and independently assessed by two otorhinolaryngologists who were blinded to CRS symptoms. CT images were scored using the mLM scoring approach.[8] All locations were scored separately for the left and right sides with the OMC scored from 0-2 (0 = no occlusion, 1 = partial occlusion, 2 = complete occlusion) and sinuses scored from 0-4 (0 = 0% opacification, 1 = 1-33%, 2 = 34-66%, 3 = 67-99%, or 4 = 100%). Nasal cavity opacification was also assessed with a score from 0-4 (0 = none, 1 = above middle turbinate, 2 = above inferior

turbinate, 3 = at or below inferior turbinate, 4 = total opacification) per side. Average scores for locations were used when otorhinolaryngologists differed by only one point, whereas adjudication by discussion and agreement was required for scores differing by greater than one point. mLM scores were also converted to traditional LM scores[4,5] (sinuses: 0 = no opacification, 1 = partial opacification, 2 = complete opacification; OMC: 0 = no occlusion and 2 = occlusion). Total LM scores were the sum of scores for all six locations.[16] Lastly, evidence of prior sinus surgery based on CT images was recorded by the otolaryngologists.

5.3.3 CRS symptoms and CRS_S index

The six core CRS_S symptoms (four symptom groups) were self-reported using a five-point Likert scale (0 = "never", 1 = "once in a while", 2 = "some of the time", 3 = "most of the time", and 4 = "all of the time") detailing frequency of symptoms experienced in the past three months. We assessed symptoms individually and combined as a CRS_S index to indicate overall NSS burden. The index followed the same logic of CRS_S and collapsed the six symptoms into four symptom groups: nasal blockage; nasal discharge (average of self-reported nasal discharge and post-nasal drip); smell loss; facial symptoms (average of self-reported facial pain and pressure). These four symptom groups were then summed to create a score ranging from 0-16.

5.3.4 Exploratory factor analysis

To evaluate whether sinus location opacification scores clustered, we first applied exploratory factor analysis (EFA), a statistical technique often used in creation of scales in which a set of observed indicators (e.g., LM scores for sinus location) allow for indirect measurement of unobservable continuous latent constructs.[17] We used maximum likelihood estimation for all models and oblique oblimin rotation to allow correlation among extracted factors. The number of extracted factors was chosen based on eigenvalues of factors[17]; sample-size adjusted Bayesian information criterion

(SSABIC)[18]; and inspection of scree-plots[17] (Supplemental material **Figure 5.8.1** and **Table 5.8.1**). In addition to these base models, nasal cavity opacification was included as a binary variable (0 = score less than one; 1= score of at least one). To assess the influence of few, large mLM/LM scores, models were estimated using categorized versions of the original scoring approaches and polychoric correlations. mLM scored locations were collapsed into three categories: 0, 1, and > 1. LM scored sinus locations were dichotomized (0 and ≥ 1).

5.3.5 Latent class analysis

We conducted latent class analysis (LCA) to identify potential subgroups of individuals based on sinus opacification patterns, as these subgroups may have clinical significance and inform pathogenesis as well as pathophysiology. LCA seeks to identify unobservable homogeneous subpopulations based on patterns of observed variable indicators[17,19]; whereas EFA determines how variables "cluster," LCA determines how people "cluster." For ease of model interpretability and identifiability, binary indicators of LM sinus scores were used in analyses (0 and ≥ 1). Increasing numbers of classes were fit and compared to guide the final LCA solution. We determined appropriateness of model fit using a variety of fit statistics, including standardized residuals, entropy, Akaike's information criterion, Bayesian information criterion (BIC), SSABIC, Pearson chi-square, Lo-Mendell-Rubin likelihood ratio test (LRT),[20,21] and bootstrapped LRT[22]. Posterior probabilities of opacification (π) were used to interpret the classes.[17]

5.3.6 Risk factors for radiologic inflammation latent classes and symptom burden

We obtained demographic information (i.e., age, sex, race/ethnicity), smoking status (never, former, current), and comorbidities used in the creation of the Charlson comorbidity index[23] from the EHR. The continuous anxiety sensitivity index (ASI)[24] measures how much a person fears the symptoms of anxiety and was included to help control for an individual's propensity to be aware of and/or over-report symptoms. We

determined migraine status at baseline using the Migraine ID questionnaire.[25] Physician diagnosis of asthma and hay fever were ascertained by self-report at baseline. Questionnaire return dates were used to categorize the season in which symptoms occurred as previously described.[14] We determined CRS_S status as previously reported.[13] Briefly, all available questionnaires up to and including the CT questionnaire were used to classify subjects as: current (met CRS_S criteria at time of CT), past (met criteria at prior timepoint but not at time of CT), or never (never met criteria). Lastly, a binary indicator was created for whether the self-reported symptoms were ascertained from a questionnaire greater than 90 days from time of CT (if the CT symptom questionnaire was not completed), a duration consistent with CRS_S guidelines.[1]

5.3.7 Other statistical analysis

5.3.7.1 *Risk factors for LCA group membership*

In an effort to better understand what types of individuals comprised these classes, we used latent class regression to identify potential risk factors for latent class membership. We assessed four separate models using a standard (i.e. "one-step") approach in which covariates can directly influence the makeup of the classes.[26] Model 1 included sex (female vs. male), ASI (z-transformed), self-reported physician diagnosis of hay fever (yes vs. no), age (z-transformed), and Charlson comorbidity index. Models 2 through 4 had the same base covariates as model 1 but further included one of self-reported physician diagnosed asthma, migraine status at baseline, or CRS_S status, respectively. As a sensitivity analysis we assessed all models with fixed latent class membership logits ensuring latent classes in the regression model matched those from the marginal LCA, using a "three-step approach".[27]

5.3.7.2 *Associations of LCA group membership with NSS*

Latent class membership (most likely based on posterior probability) was used as an indicator variable in subsequent analyses of overall NSS burden and individual

symptoms. For modeling associations of LCA and selected covariates with NSS, we used least absolute deviation regression of the conditional median (sometimes referred to as quantile or median regression).[28,29] Model building included fitting unadjusted models for a pool of potential risk factors selected *a priori* based on our prior work with CRS.[13,14,30-33] Variables were selected for the final model if they were theoretically and/or statistically associated with NSS burden or were a demonstrated confounder of the association of latent class with NSS. Standard errors as well as bias-corrected and accelerated 95% confidence intervals were estimated via bootstrapping, with acceleration correcting for skewness in the bootstrap distribution.[34]

For associations with individual symptoms we used multivariate (multiple outcome) ordered probit models.[35-38] Probit regression is similar to logistic regression, however the former uses an inverse normal link function while the latter uses a logit link function.[39] Only four subjects reported nasal discharge in the highest frequency category (all of the time), so we combined that category with the one below (most of the time). We assessed potential influence of observations for each symptom's unique model, from which three observations were deemed likely influential. As a sensitivity analysis, we assessed the final multivariate model with these observations removed, to better determine whether they had an impact on the final estimates.

EFA, LCA, and latent class regression were fit using Mplus v.8.1 (Muthén & Muthén, Los Angeles, CA) whereas all other models were fit using STATA v.15.1 (StataCorp, College Station, TX, USA).

5.4 Results

5.4.1 Overview of study sample

In our sample of 646 subjects, 18.6% (n = 120) had radiologic evidence of prior sinus surgery. Comparing those with surgery ("surgical") to those without ("non-surgical), surgical subjects were more likely to: be male, self-report physician diagnosed asthma,

meet current CRS_S status, and have higher median LM and mLM scores (**Table 5.4.1.1**). Subjects with evidence of prior sinus surgery were excluded from subsequent analysis given the inability to determine whether prior sinus surgery affected 1) observed sinus opacification and 2) self-reported symptoms.

Table 5.4.1.1. Study sample characteristics comparing subjects with and without evidence of prior sinus surgery on sinus computed tomography

Variables	Non-surgical (n = 526)	Surgical (n = 120)
	Median (IQR, range)	
Age at baseline (in years)	56.4 (17.3, 19.1 – 85.7)	58.2 (15.3, 22.6 – 88.1)
Body mass index (BMI; kg/m^2)	30.0 (8.73, 17.5 – 59.3)	30.9 (7.62, 15.7 – 51.2)
Charlson comorbidity index	2.00 (2.00, 0 – 7)	2.00 (3.00, 0 – 7)
Anxiety sensitivity index (0 – 64)	12.0 (16.0, 0 – 64)	13.0 (17.5, 0 – 52)
Lund-Mackay (0 – 24)	0.00 (2.00, 0 – 22)	3.00 (6.00, 0 – 22)***
Modified Lund-Mackay (0 – 44)	1.50 (3.00, 0 – 39.5)	4.50 (9.00, 0 – 42)***
	Column proportion (SE)	
Female sex, n = 431	0.69 (0.02)	0.56 (0.05)**
Non-white race/ethnicity, n = 26	0.05 (0.01)	0.00 (0.00)
Medical Assistance (ever received)[a], n = 56	0.09 (0.01)	0.08 (0.02)
CRS_S status[b]		
Never, n = 73	0.13 (0.01)	0.04 (0.02)***
Past, n = 249	0.39 (0.21)	0.37 (0.04)
Current, n = 324	0.48 (0.02)	0.59 (0.04)*
Self-reported physician diagnosis of asthma, n = 197	0.27 (0.02)	0.44 (0.05)***
Self-reported physician diagnosed of hay fever, n = 361	0.55 (0.02)	0.61 (0.04)
Migraine headache status[c], n = 229	0.36 (0.02)	0.33 (0.04)

***p-value < 0.001, **p-value < 0.01, *p-value < 0.05; p-values determined by Mann-Whitney-Wilcoxon U-test or Wald test.

Abbreviations: CRS_S = European Position Paper on Rhinosinusitis subjective symptoms definition for CRS classification; CT = computed tomography; EHR = electronic health record

[a] Medical Assistance was determined from the EHR as a proxy for family socioeconomic status.

[b] CRS status determined using self-reported symptoms relevant to CRS_S at all observed time-points up to and including closest to time of CT scan; never CRS = never met CRS_S criteria over follow-up; past CRS = met CRS_S criteria at some point in lifetime or over follow-up, but did not meet criteria at time of CT scan; current CRS = met CRS_S criteria at time of CT scan.

[c] Based on responses to four questions, at baseline, from the ID Migraine questionnaire.

5.4.2 LM vs. mLM scoring and nasal cavity opacification

Analysis of location-specific opacification scores using EFA showed both LM and mLM measure just one underlying construct (Supplemental material **Table 5.8.1** and **Figure 5.8.1**). No meaningful differences with respect to factor composition were observed (i.e. for LM and mLM, all sinuses contributed to the underlying construct); however, frontal and sphenoid locations had larger factor loadings (i.e. more strongly associated with the underlying construct) when measured via LM (Supplemental material **Table 5.8.2**).

5.4.3 How should location specific scores be used?

Given EFA models showed no differences between scoring approaches, LM was used for all subsequent analyses because of its widespread use in prior literature and clinical settings. LCA revealed that a three class model had superior fit to the one and two class models (**Table 5.4.3.1**). The three classes were identifiable as “no/mild opacification, “localized opacification,” and “diffuse opacification” with prevalence estimates of 63.0%, 21.5%, and 15.5%, respectively (**Table 5.4.3.2**). Descriptive characteristics of individuals assigned to each class showed substantial differences in median LM scores with the no/mild class having a score of 0, localized a score of 1, and diffuse a score of 7 (**Table 5.4.3.2**). Further, 94% of subjects assigned to the diffuse class had an LM score of 3 or greater, compared to 21.0% and 0.3% in the localized and no/mild classes, respectively.

Table 5.4.3.1. Lund-Mackay sinus opacification patterns and latent class analyses fits (one to three classes)

Lund-Mackay sinus opacification score (in order): OMC, maxillary (M), anterior ethmoid (AE), posterior ethmoid (PE), frontal (F), and sphenoid (S): None (0) or at least 1 (1)								**Expected pattern frequency (standardized residual)**		
	OMC	**M**	**AE**	**PE**	**F**	**S**	**Observed, n**	**1-class model**	**2-class model**	**3-class model**
8 most frequently observed patterns (84.8% of subjects)	0	0	0	0	0	0	265	159.3 (10.0)	253.7 (0.99)	264 (0.09)
	0	1	0	0	0	0	94	100.9 (-0.76)	104.8 (-1.18)	94.7 (-0.08)
	0	1	1	0	0	0	26	31.1 (-0.95)	14.88 (2.92)	26 (0.10)
	0	0	1	0	0	0	19	49.1 (-4.51)	27.3 (-1.63)	19 (-0.09)
	1	1	1	1	0	0	12	0.67 (13.87)	11.3 (0.20)	10.7 (0.39)
	0	0	0	0	0	1	11	12.4 (-0.40)	8.06 (1.04)	10.8 (0.05)
	1	1	0	0	0	0	11	13.2 (-0.62)	3.44 (4.09)	10.3 (0.23)
	1	1	1	1	1	1	8	0.0 (117.5)	3.45 (2.46)	3.94 (2.05)
Latent class model fit statistics										
Entropy								NA	0.91	0.86
AIC								2664.4	2196	2172.8
BIC								2690.0	2251.4	2258.1
SSABIC								2671.0	2210.1	2194.6
Pearson chi-square								1955.2 ($p < 0.0001$)	75.9 ($p = 0.01$)	36.8 ($p = 0.73$)
Vuong-Lo-Mendell-Rubin LRT								NA	482.5 ($p < 0.0001$)	36.4 ($p < 0.0001$)
Bootstrapped LRT								NA	482.5 ($p < 0.0001$)	37.2 ($p< 0.0001$)
Latent class prevalence (estimated from model)										
Class 1								100%	83.5%	63.0%
Class 2									16.5%	21.5%
Class 3										15.5%

Abbreviations: AIC = Akaike's information criterion; BIC = Bayesian information criterion; SSABIC = sample size-adjusted Bayesian information criterion; LRT = likelihood ratio test; OMC = osteomeatal complex

Table 5.4.3.2. Latent class posterior probabilities of sinus opacification and class membership characteristics for selected variables

Sinus and OMC	Lund-Mackay sinus opacification score[a] > 0 (overall %)	Sinus opacification probability		
		Class 1	Class 2	Class 3
OMC	11.6	0.40	11.6	56.8
Maxillary	38.8	6.60	100	85.0
Anterior ethmoid	23.6	6.70	22.2	93.9
Posterior ethmoid	14.1	3.50	0.00	76.5
Frontal	8.20	1.10	2.00	45.5
Sphenoid	7.20	3.90	0.00	30.5
Class prevalence (%)[b]		63.0%	21.5%	15.5%
Class name		No/mild opacification	Localized opacification	Diffuse opacification
Mean / median LM score (min, max)		0.18 / 0 (0, 4)	1.8 / 1 (1, 6)	7.2 / 7 (2, 22)
% LM ≥ 2		3%	44%	100%
% LM ≥ 3		0%	21%	94%
% LM ≥ 4		0%	9%	89%
% LM ≥ 5		0%	2%	78%
% female sex		74%	60%	54%
% migraine headache status[c]		37%	38%	30%
% self-reported physician diagnosis of hay fever		53%	59%	57%
% self-reported physician diagnosis of asthma		27%	24%	33%
% current CRS_S[d]		49%	43%	54%
% past CRS_S		39%	44%	33%
% any nasal cavity opacification (row %)		0%	0%	100%

Abbreviations: CRS_S = European Position Paper on Rhinosinusitis subjective symptoms definition for CRS classification; LM = Lund-Mackay; OMC = osteomeatal complex

[a] Based on CT scoring by two otorhinolaryngologists blinded to CRS_S status.

[b] Based on estimated model.

[c] Based on responses to four questions, at baseline, from the ID Migraine questionnaire.

[d] CRS status determined using self-reported symptoms relevant to CRS_S at all observed time-points up to and including closest to time of CT scan; never CRS = never met CRS_S criteria over follow-up; past CRS = met CRS_S criteria at some point in lifetime or over follow-up, but did not meet criteria at time of CT scan; current CRS = met CRS_S criteria at time of CT scan.

5.4.4 Risk factors for latent class membership

For all models (Supplemental material **Tables 5.8.3** and **5.8.4** one-step and three-step approaches, respectively), female sex was the only risk factor to cross an inferential boundary, with females (compared to males) having a 63-66% reduction in relative risk of being in the diffuse class (vs. no/mild) (Supplemental material **Tables 5.8.3 and 5.8.4**). There were also elevated relative risks for self-reported physician diagnosis of hay fever for localized and diffuse (vs. no/mild), self-reported physician diagnosis of asthma for diffuse (vs. no/mild), and migraine headache for localized (vs. no/mild); however, these 95% confidence intervals included 1.0 (i.e. did not reach statistical significance) (Supplemental material **Tables 5.8.3 and 5.8.4**).

5.4.5 Latent class membership informing LM score cutoff selection

We compared the distributions of LM scores in each class using LM cutoffs of ≥ 4 and ≥ 3 (**Figure 5.4.5.1**). LM ≥ 4 tended to exclude individuals in the diffuse class more severely than LM ≥ 3. While LM ≥ 3 still excluded individuals in the diffuse class (n = 5),

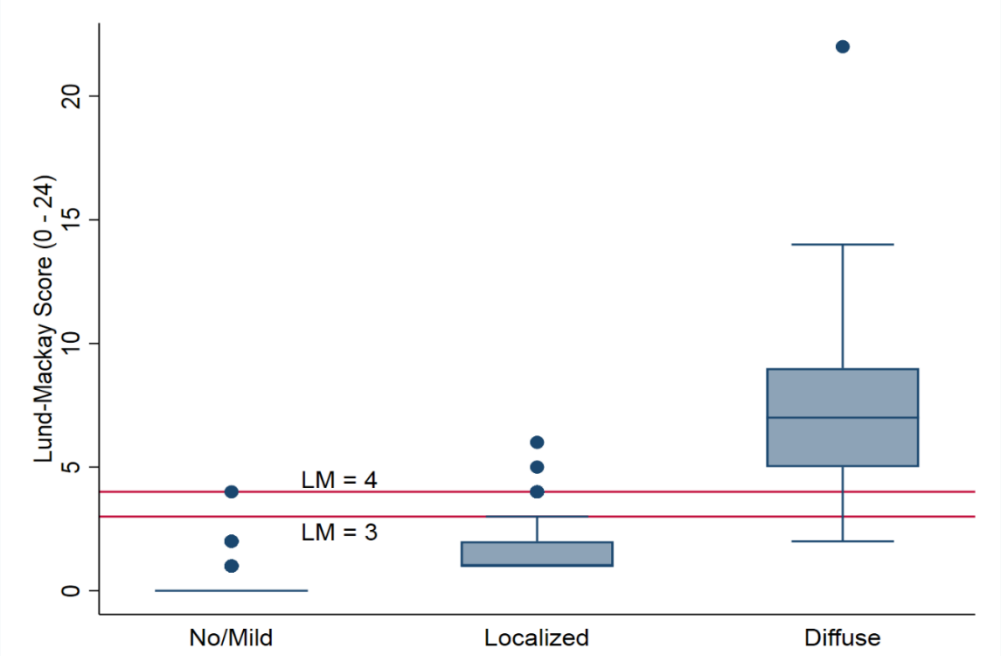

Figure 5.4.5.1. Lund-Mackay distributions within latent classes using two different LM cutoffs (4 and 3, identified with two horizontal red lines on plot).

it provided a balance of including subjects from the diffuse class (94%) while also excluding 99.7% of the no/mild class and 79% of localized.

5.4.6 Associations of latent class with overall symptom burden and core CRS_S symptoms

The distribution of total NSS burden scores was shifted to higher values for the diffuse class (Supplemental material **Figure 5.8.2**). In adjusted analysis, diffuse opacification (vs. no/mild) was associated with more NSS, with a median index value increase of 1.15 (95% confidence interval: 0.29, 2.02) (**Table 5.4.6.1**). As an example, this represents subjects in the diffuse class reporting one of the four symptom groups at a frequency one category higher than the other two classes (e.g. most of the time vs. some of the time), on average.

For individual symptoms, diffuse opacification was positively associated with nasal blockage ($\beta = 0.27$; 95% confidence interval: 0.01, 0.53) and smell loss ($\beta = 0.37$; 95% confidence interval: 0.10, 0.63) (**Table 5.4.6.2**), conferring increased probability of reporting symptoms (Supplemental material **Figure 5.8.3**). Migraine headache modified associations of localized latent class membership with nasal discharge and post-nasal drip by reducing the probability of reporting these symptoms (Supplemental material **Figure 5.8.4**). In a sensitivity analysis, three potentially influential observations were removed prior to model estimation; effect estimates were not substantively changed (Supplemental material **Table 5.8.5**)

Table 5.4.6.1. Associations of selected variables with CRS_S symptom index[a] at the median (0.50 quantile)

Variables	β-coefficient (BCa[b] confidence interval)
Latent class (vs. no/mild)	
Localized	0.01 (-0.74, 0.61)
Diffuse	1.15 (0.29, 2.02)*
Female sex (vs. male)	-0.24 (-1.06, 0.31)
Anxiety sensitivity index (z-transformed)	0.55 (0.22, 0.94)*
Migraine headache status (vs. no)[c]	1.10 (0.56, 1.82)*
Self-reported physician diagnosis of hay fever (vs. no)	0.50 (-0.12, 1.12)
Season questionnaire returned (vs. fall)[d]	
Winter	0.50 (-0.42, 1.35)
Spring	0.54 (-0.24, 1.30)
Summer	0.18 (-0.63, 1.22)

* Crossed inferential boundary (evidenced by confidence interval not crossing 0.00); model additionally adjusted for smoking status (former or current vs. never) at baseline and binary indicator for whether symptoms taken from questionnaire occurred > 90 days from time of CT scan.
Abbreviations: BCa = bias-corrected and accelerated; CRS_S = European Position Paper on Rhinosinusitis subjective symptoms definition for CRS classification;
[a] Sum of 4 core CRS_S symptom groups (nasal blockage; nasal discharge and post-nasal drip; smell loss; facial pain and facial pressure) self-reported at questionnaire closest to time of CT scan.
[b] 95% bias-corrected and accelerated confidence interval based on bootstrap estimation; adjusted for skew of bootstrap distribution.
[c] Based on responses to four questions, at baseline, from the ID Migraine questionnaire.
[d] Fall = 22 September to 21 December; winter = 22 December to 21 March; spring = 22 March to 22 June; summer = 22 June to 21 September.

Table 5.4.6.2. Associations of selected variables with six core CRS_S symptoms in multivariate (multiple-outcome) ordered probit[a] regression

Variables	NB	ND[b]	PND[c]	SL	FPN[d]	FPR[e]
Latent class (vs. no/mild)						
Localized	-0.06 (-0.28, 0.16)	0.10 (-0.17, 0.37)	0.12 (-0.15, 0.39)	-0.04 (-0.26, 0.19)	-0.12 (-0.34, 0.09)	-0.10 (-0.32, 0.11)
Diffuse	0.27 (0.01, 0.53)*	0.25 (-0.06, 0.56)	-0.07 (-0.38, 0.24)	0.37 (0.10, 0.63)**	0.07 (-0.19, 0.33)	0.08 (-0.18, 0.34)
Migraine headache (vs. no)[f]	0.23 (0.03, 0.43)*	0.27 (0.02, 0.52)*	0.10 (-0.15, 0.35)	0.30 (0.10, 0.50)**	0.49 (0.29, 0.70)***	0.46 (0.25, 0.66)***
Latent class by migraine status at baseline interaction						
Localized		-0.55 (-0.97, -0.12)*	-0.63 (-1.10, -0.20)**			
Diffuse		-0.02 (-0.54, 0.50)	0.31 (-0.24, 0.85)			

***p-value < 0.001, **p-value < 0.01, *p-value < 0.05;
Abbreviations: CRS_S = European Position Paper on Rhinosinusitis subjective symptoms definition for CRS classification; FPN = facial pain; FPR = facial pressure; NB = nasal blockage; ND = anterior nasal discharge; PND = post-nasal drip; SL = smell loss
[a] Ordered probit regression yielded β-coefficients which represented a β-change in z-score of underlying outcome scale; all models adjusted for season, female sex, ASI, migraine status, and binary indicator for whether symptoms taken from questionnaire occurred > 90 days from time of CT scan.
[b] Additionally included ASI^2 and interactions for female sex by ASI and ASI^2.
[c] Additionally included self-reported physician diagnosis of hay fever, age, and interactions for female sex by ASI and by age.
[d] Additionally included age, age^2, Charlson comorbidity index, binary indicator for receipt of Medical Assistance, ASI^2, and interactions for female sex by ASI and ASI^2.
[e] Additionally included self-reported physician diagnosed hay fever, age, and age^2.
[f] Based on responses to four questions, at baseline, from the ID Migraine questionnaire.

5.5 Discussion

Improving and standardizing measurement of sinus opacification is critical to advancing research in CRS as inconsistent or weakly-justified approaches to characterizing sinus opacification makes inferences across studies difficult. To the best of our knowledge, this is first study to evaluate LM vs. mLM, evaluate whether nasal cavity opacification should be included in the two scoring approaches, and identify other ways to classify location-specific scores, in a general population representative sample.

LM has been recommended by the Task Force on Rhinosinusitis due to its simplicity and ease in interpretation[5]; although, inability to assess progression of disease prompted the development of modified scoring approaches including the mLM system.[8] A previous study of LM, mLM, and Zinreich scoring approaches found no conclusive evidence that the modified approaches were an improvement to LM, vis-à-vis agreement between visual scoring by otorhinolaryngologists and computer calculated scoring (via soft tissue density rates).[7] Yet, no prior studies had evaluated their comparative utility in a general population sample of non-surgical candidates representing a broad spectrum of disease. Since both EFA models found a single factor, to which all locations were associated, we found no advantage of using mLM over LM in research of sinus diseases.

Neither mLM nor LM includes nasal cavity opacification as part of its scoring, but opacification in the nasal cavity might be indicative of nasal polyposis, an important pathology of CRSwNP.[1] While we found no evidence that inclusion of nasal cavity opacification in scoring added information beyond that provided by the other sinus locations (all subjects with nasal cavity opacification were in the diffuse class), we had relatively few persons with any nasal cavity opacification in our sample (5.3% of the original 646 sample). Therefore, a larger study with greater representation of CRSwNP

should be performed to more definitively address whether nasal cavity opacification should be included in scoring approaches.

Whereas our EFA models showed all sinuses to measure the same underlying construct (i.e. inflammation), LCA identified three subpopulations of sinus opacification: no opacification or mild, isolated opacification; localized maxillary opacification; and diffuse opacification, almost always including the anterior ethmoid, indicating that patterns of radiologic inflammation differ among people. Therefore, current approaches to summing scores across all sinus locations may hide clinically useful information about the location and pattern of opacification. Our patterns of opacification share similarities with a prior study of sinus CT scans.[40] In that study, five mutually inclusive patterns of sinonasal disease were observed among 500 patients from a tertiary care setting, whom were under evaluation for suspected sinus disease and possible candidates for surgical intervention. The patterns were: limited maxillary sinus disease; diffuse anterior disease; posterior sinus disease; sinonasal polyposis; and limited disease without involvement of the osteomeatal unit or sphenoethmoidal recess.[40] Our study, however, addresses many limitations of that study: we used subjects selected from the general population, rather than a tertiary care population likely representing only the most severe end of the disease spectrum; we used a well-known and recommended scoring approach (LM) for quantifying sinus opacification; also, our study used formal statistical methods to discriminate patterns, identifying mutually exclusive subgroups of individuals. While our latent classes may appear hierarchical (i.e. represent points along disease progression), this cannot be determined without longitudinal CT information to assess whether individuals transition in or out of these latent classes.

Risk factors for latent class membership provided insight into the clinical or pathological significance of the classes. Male sex has previously been associated with

larger LM scores,[41] a finding supported by our latent classes in which males were over 2.5 times more likely to be in the diffuse (vs. no/mild) class than females. Hay fever and asthma both trended towards an association with the diffuse class, both of which have previously been associated with the occurrence of diagnostic codes for CRS,[30,31] CRS symptoms (CRS_S),[13,42] and sinus opacification on CT imaging.[41,43] Future studies should explore whether latent class membership is associated with CRS endotypes and response to treatment as these classes could have relevance to disease management.

These subgroups suggested that a different approach to the use of location-specific sinus opacification may offer advantages over a single-score cutoff. The current suggested guideline for objective evidence indicative of CRS is an LM cutoff of LM ≥ 4,[6] however there are several limitations with the study from which that guideline was established. That study used CT scans from subjects with indications requiring CT imaging, therefore they do not necessarily represent the general population. Further, individuals with suspected or confirmed CRS were excluded from the analysis, thereby making the distribution of LM scores in the target sample unavailable. However, if the standard approach to a single LM score cutoff is to be used a cutoff of LM ≥ 3 may be more appropriate, given its greater inclusion of individuals from the diffuse opacification class, which is taken to represent the most sinus diseased group of individuals.

Lastly, we saw an opportunity to address the oft-cited lack of correlation between objective and subjective evidences of CRS. Our first novel insight to this dilemma came from an appreciation of the causal relation of inflammation and symptoms. NSS cannot cause sinus inflammation, but inflammation could cause NSS; as such, we reversed the directionality of our tested associations to allow sinus opacification latent classes to predict NSS. In adjusted analysis, diffuse latent class membership was associated with overall NSS burden; however, this overall association seemed to be primarily driven by

associations with nasal blockage and smell loss. Although this had never been evaluated in a general population representative sample across a broad spectrum of disease and in the appropriate causal direction, these findings are supported by prior studies in tertiary care settings. For example, a study using CT scans from subjects presenting with CRS symptoms at an otorhinolaryngology care clinic found subjects with LM ≥ 4 were more likely to report smell loss. [44] A similar finding was observed among subjects with non-CRS related indications requiring sinus CT imaging, in which LM ≥ 4 was associated with more nasal blockage and smell loss.[41]

Our study has several strengths. We used a population-based sample generalizable to the population in the region that included non-surgical patients representing a spectrum of individuals typically excluded from CT-based studies of CRS, to determine whether mLM offers advantages over LM; whether nasal cavity opacification should be included in scoring; and used novel approaches to categorizing location-specific CT opacification scores We also identified subgroups of sinus opacification that may have clinical and epidemiologic relevance. This study, however, is not without limitations. Due to sample size and model identifiability we were unable to assess LCA models beyond sinus opacification patterns based on presence/absence of opacification. Thus, we could not identify subgroups which also described severity of disease (e.g., unilateral vs. bilateral).

5.6 Conclusion

Overall, we found no differences between mLM and LM scoring approaches for sinus CT opacification and no additional benefit from including nasal cavity opacification as part of either scoring approach. We identified three subgroups of sinus opacification suggesting the use of a single-score cutoff as criteria for objective evidence of CRS is likely inappropriate. These three subgroups may represent different disease

pathogeneses and therefore additional work is needed to establish their clinical relevance.

5.7 References

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Table 5.8.1. Fit of exploratory factor analysis models of modified Lun-Mackay (mLM) and Lund-Mackay (LM) scored sinuses. Models were performed on original and categorized (reduced) scales, with and without addition of binary (none vs. at least a score of one) nasal cavity opacification.

	No nasal cavity included		**Nasal cavity included**	
	Original scale	**Categorized scale**	**Original scale**	**Categorized scale**
mLM scale				
SSABIC				
1 factor	6730.4	4342.3	6969.1	4407.6
2 factor	-	4322.4	-	4390.0
Eg > 1.0	1	1	1	1
LM scale				
SSABIC				
1 factor	2890.9	2196.4	2940.3	2240.7
2 factor	-	2192.7	2929.9	2238.2
Eg > 1.0	1	1	1	1

Abbreviations: Eg = eigenvalue; LM = Lund-Mackay; mLM = modified Lund-Mackay; SSABIC = sample size-adjusted Bayesian information criterion

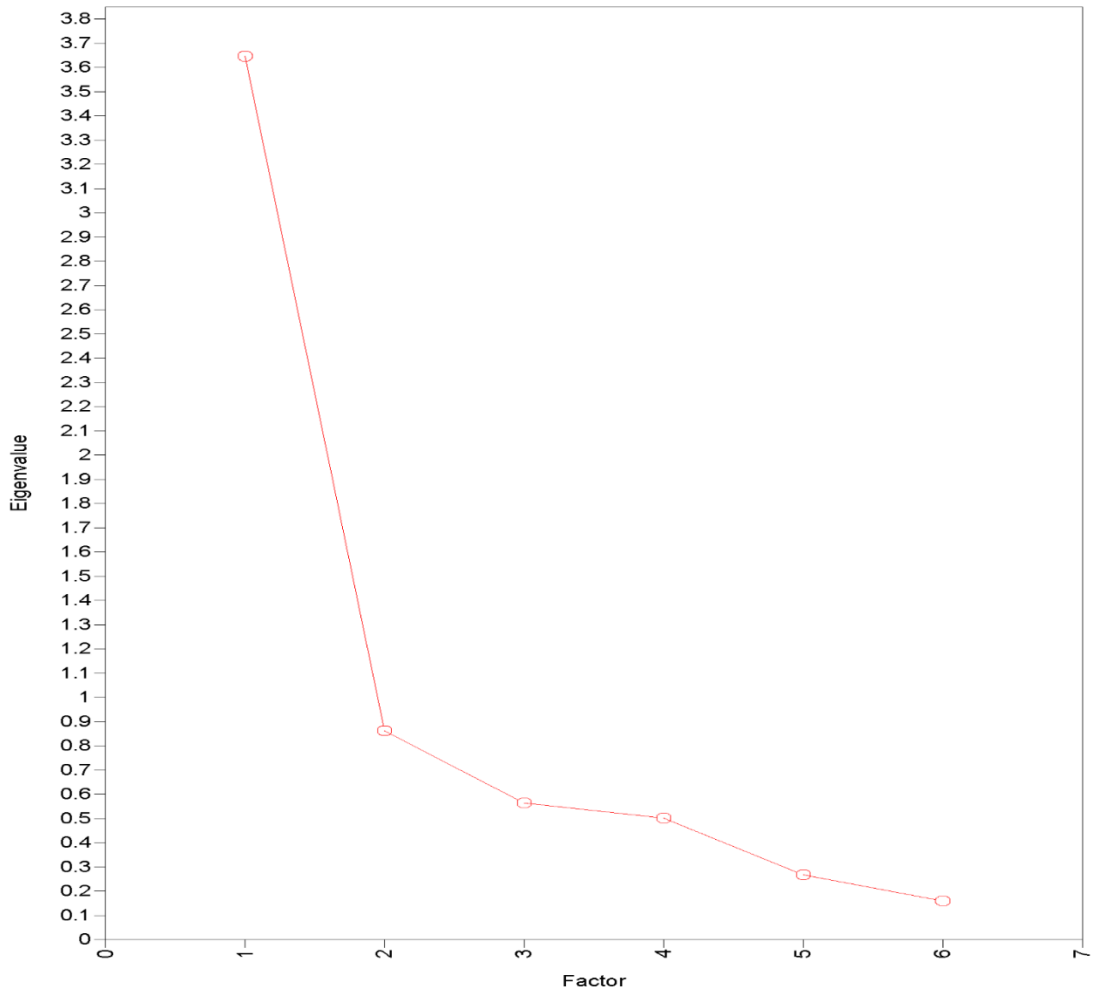


Figure 5.8.1. Example scree plot for exploratory factor analysis models. Scree plot from modified Lund-Mackay scored locations in the raw (uncategorized) scale and no nasal cavity opacification. All scree plots were similar to the one shown above. Larger eigenvalues indicate greater variance explained by the associated factor.

Table 5.8.2. One factor exploratory factor analysis models of modified Lund-Mackay (mLM) and Lund-Mackay (LM) scored sinuses. Models were performed on original and categorized (reduced) scales, with and without addition of binary (none vs. at least a score of one) nasal cavity opacification.

Sinus location	No nasal cavity included				Nasal cavity included			
	Original scale		Categorized scale		Original scale		Categorized scale	
	Loading	Communality	Loading	Communality	Loading	Communality	Loading	Communality
mLM OMC	0.80	0.63	0.80	0.65	0.89	0.80	0.80	0.65
Maxillary	0.67	0.45	0.64	0.41	0.75	0.57	0.64	0.41
Anterior ethmoid	0.94	0.89	1.00	1.00	0.97	0.94	1.00	1.00
Posterior ethmoid	0.81	0.66	0.83	0.69	0.86	0.74	0.83	0.69
Frontal	0.71	0.51	0.75	0.56	0.77	0.60	0.75	0.56
Sphenoid	0.34	0.12	0.47	0.22	0.40	0.16	0.47	0.22
Nasal cavity					0.66	0.44	0.78	0.60

LM OMC	0.85	0.72	0.84	0.71	0.84	0.71	0.83	0.70
Maxillary	0.72	0.52	0.65	0.42	0.72	0.52	0.66	0.44
Anterior ethmoid	0.90	0.81	0.92	0.85	0.90	0.81	0.92	0.84
Posterior ethmoid	0.91	0.83	0.85	0.72	0.91	0.82	0.85	0.72
Frontal	0.85	0.73	0.86	0.74	0.85	0.73	0.85	0.72
Sphenoid	0.61	0.37	0.61	0.37	0.62	0.39	0.61	0.37
Nasal cavity					0.87	0.75	0.93	0.86
Abbreviations: LM = Lund-Mackay; mLM = modified Lund-Mackay; OMC = osteomeatal complex								

Table 5.8.3. Unadjusted and adjusted associations of selected variables with latent class membership using the one-step[a] method

Variables	No/mild	Relative risk ratios (RRR) and 95% confidence intervals			
		Localized		Diffuse	
		Unadjusted	Adjusted	Unadjusted	Adjusted
Model 1					
Female sex (vs. male)	REF	0.58 (0.23, 1.46)	0.55 (0.19, 1.64)	0.37 (0.21, 0.63)***	0.34 (0.19, 0.60)***
Anxiety sensitivity index (z-transformed)	REF	0.89 (0.70, 1.11)	0.89 (0.65, 1.22)	0.97 (0.77, 1.23)	0.98 (0.77, 1.25)
Self-reported physician diagnosis of hay fever (vs. no)	REF	1.36 (0.80, 2.31)	1.64 (0.82, 3.29)	1.28 (0.75, 2.18)	1.49 (0.86, 2.57)
Age (years; z-transformed)	REF	1.06 (0.80, 1.40)	1.05 (0.71, 1.55)	0.94 (0.73, 1.22)	0.91 (0.69, 1.20)
Charlson comorbidity index (z-transformed)	REF	0.93 (0.71, 1.21)	0.91 (0.64, 1.29)	0.88 (0.67, 1.17)	0.91 (0.67, 1.23)
Model 2					
Female sex (vs. male)	REF	0.58 (0.23, 1.46)	0.63 (0.38, 1.07)	0.37 (0.21, 0.63)***	0.34 (0.20, 0.60)***
Anxiety sensitivity index (z-transformed)	REF	0.89 (0.70, 1.11)	0.90 (0.71, 1.13)	0.97 (0.77, 1.23)	0.97 (0.76, 1.25)
Self-reported physician diagnosis of hay fever (vs. no)	REF	1.36 (0.80, 2.31)	1.59 (1.00, 2.53)	1.28 (0.75, 2.18)	1.40 (0.80, 2.46)
Age (years; z-transformed)	REF	1.06 (0.80, 1.40)	1.02 (0.80, 1.29)	0.94 (0.73, 1.22)	0.92 (0.70, 1.21)
Charlson comorbidity index (z-transformed)	REF	0.93 (0.71, 1.21)	0.98 (0.75, 1.26)	0.88 (0.67, 1.17)	0.86 (0.64, 1.15)
Self-reported physician diagnosis of asthma (vs. no)	REF	0.79 (0.48, 1.31)	0.75 (0.42, 1.32)	1.31 (0.75, 2.28)	1.45 (0.79, 2.65)

Model 3					
Female sex (vs. male)	REF	0.58 (0.23, 1.46)	0.50 (0.06, 4.06)	0.37 (0.21, 0.63)***	0.36 (0.20, 0.64)***
Anxiety sensitivity index (z-transformed)	REF	0.89 (0.70, 1.11)	0.89 (0.57, 1.41)	0.97 (0.77, 1.23)	1.00 (0.77, 1.29)
Self-reported physician diagnosis of hay fever (vs. no)	REF	1.36 (0.80, 2.31)	1.62 (0.71, 3.72)	1.28 (0.75, 2.18)	1.49 (0.86, 2.59)
Age (years; z-transformed)	REF	1.06 (0.80, 1.40)	1.11 (0.52, 2.35)	0.94 (0.73, 1.22)	0.88 (0.66, 1.16)
Charlson comorbidity index (z-transformed)	REF	0.93 (0.71, 1.21)	0.89 (0.53, 1.51)	0.88 (0.67, 1.17)	0.91 (0.67, 1.24)
Migraine headache status (vs. no)[b]	REF	1.13 (0.68, 1.89)	1.38 (0.50, 3.79)	0.65 (0.36, 1.18)	0.72 (0.37, 1.40)
Model 4					
Female sex (vs. male)	REF	0.58 (0.23, 1.46)	0.52 (0.11, 2.46)	0.37 (0.21, 0.63)***	0.33 (0.19, 0.59)***
Anxiety sensitivity index (z-transformed)	REF	0.89 (0.70, 1.11)	0.92 (0.61, 1.38)	0.97 (0.77, 1.23)	0.96 (0.75, 1.23)
Self-reported physician diagnosis of hay fever (vs. no)	REF	1.36 (0.80, 2.31)	1.73 (0.69, 4.34)	1.28 (0.75, 2.18)	1.48 (0.84, 2.60)
Age (years; z-transformed)	REF	1.06 (0.80, 1.40)	1.07 (0.68, 1.70)	0.94 (0.73, 1.22)	0.90 (0.68, 1.19)
Charlson comorbidity index (z-transformed)	REF	0.93 (0.71, 1.21)	0.90 (0.61, 1.34)	0.88 (0.67, 1.17)	0.90 (0.67, 1.22)
CRS_S status (vs. never CRS_S)[c] Past CRS_S Current CRS_S	REF	 1.11 (0.50, 2.46) 0.82 (0.38, 1.81)	 1.10 (0.36, 3.33) 0.84 (0.32, 2.23)	 0.76 (0.33, 1.74) 1.02 (0.47, 2.22)	 0.73 (0.30, 1.74) 1.03 (0.45, 2.38)

***p-value < 0.001, **p-value < 0.01, *p-value < 0.05
Abbreviations: CRS_S = European Position Paper on Rhinosinusitis subjective symptoms definition for CRS classification
[a] Did not fix measurement error associated with latent class membership allowing covariates to influence makeup of latent classes.
[b] Based on responses to four questions, at baseline, from the ID Migraine questionnaire.
[c] CRS status determined using self-reported symptoms relevant to CRS_S at all observed time-points up to and including closest to time of CT scan; never CRS = never met CRS_S criteria over follow-up; past CRS = met CRS_S criteria at some point in lifetime or over follow-up, but did not meet criteria at time of CT scan; current CRS = met CRS_S criteria at time of CT scan.

Table 5.8.4. Unadjusted and adjusted associations of selected variables with latent class membership using the three-step[a] method

Variable	No/Mild	Relative risk ratios (RRR) and 95% confidence intervals			
		Localized		Diffuse	
		Unadjusted	Adjusted	Unadjusted	Adjusted
Model 1					
Sex (female vs. male)	REF	0.69 (0.41, 1.48)	0.67 (0.40, 1.13)	0.39 (0.23, 0.66)***	0.36 (0.20, 0.62)***
Anxiety sensitivity index (z-transformed)	REF	0.88 (0.68, 1.13)	0.89 (0.68, 1.15)	0.96 (0.76, 1.22)	0.98 (0.77, 1.24)
Self-reported physician diagnosis of hay fever	REF	1.32 (0.82, 2.13)	1.47 (0.89, 2.42)	1.19 (0.71, 2.01)	1.41 (0.82, 2.42)
Age (years; z-transformed)	REF	1.04 (0.81, 1.34)	1.04 (0.80, 1.35)	0.91 (0.71, 1.18)	0.87 (0.66, 1.15)
Charlson comorbidity index (z-transformed)	REF	0.92 (0.72, 1.18)	0.91 (0.70, 1.18)	0.90 (0.67, 1.19)	0.94 (0.69, 1.28)
Model 2					
Sex (female vs. male)	REF	0.69 (0.41, 1.48)	0.67 (0.40, 1.12)	0.39 (0.23, 0.66)***	0.36 (0.21, 0.62)***
Anxiety sensitivity index (z-transformed)	REF	0.88 (0.68, 1.13)	0.89 (0.68, 1.15)	0.96 (0.76, 1.22)	0.97 (0.76, 1.23)
Self-reported physician diagnosis of hay fever	REF	1.32 (0.82, 2.13)	1.53 (0.92, 2.54)	1.19 (0.71, 2.01)	1.32 (0.75, 2.32)
Age (years; z-transformed)	REF	1.04 (0.81, 1.34)	1.03 (0.78, 1.34)	0.91 (0.71, 1.18)	0.89 (0.68, 1.17)
Charlson comorbidity index (z-transformed)	REF	0.92 (0.72, 1.18)	0.95 (0.71, 1.28)	0.90 (0.67, 1.19)	0.88 (0.65, 1.20)
Self-reported physician diagnosis of asthma	REF	0.80 (0.46, 1.39)	0.79 (0.42, 1.44)	1.29 (0.74, 2.25)	1.42 (0.78, 2.58)

Model 3					
Sex (female vs. male)	REF	0.69 (0.41, 1.48)	0.64 (0.38, 1.10)	0.39 (0.23, 0.66)***	0.37 (0.21, 0.64)***
Anxiety sensitivity index (z-transformed)	REF	0.88 (0.68, 1.13)	0.88 (0.68, 1.13)	0.96 (0.76, 1.22)	0.99 (0.78, 1.26)
Self-reported physician diagnosis of hay fever	REF	1.32 (0.82, 2.13)	1.47 (0.89, 2.41)	1.19 (0.71, 2.01)	1.41 (0.82, 2.42)
Age (years; z-transformed)	REF	1.04 (0.81, 1.34)	1.07 (0.81, 1.43)	0.91 (0.71, 1.18)	0.85 (0.65, 1.13)
Charlson comorbidity index (z-transformed)	REF	0.92 (0.72, 1.18)	0.91 (0.70, 1.18)	0.90 (0.67, 1.19)	0.94 (0.69, 1.28)
Migraine headache status (vs. no)[b]	REF	1.09 (0.68, 1.77)	1.26 (0.75, 2.11)	0.73 (0.41, 1.28)	0.81 (0.44, 1.48)
Model 4					
Sex (female vs. male)	REF	0.69 (0.41, 1.48)	0.68 (0.40, 1.13)	0.39 (0.23, 0.66)***	0.35 (0.20, 0.61)***
Anxiety sensitivity index (z-transformed)	REF	0.88 (0.68, 1.13)	0.91 (0.70, 1.18)	0.96 (0.76, 1.22)	0.96 (0.75, 1.22)
Self-reported physician diagnosis of hay fever	REF	1.32 (0.82, 2.13)	1.50 (0.91, 2.46)	1.19 (0.71, 2.01)	1.40 (0.80, 2.45)
Age (years; z-transformed)	REF	1.04 (0.81, 1.34)	1.04 (0.80, 1.35)	0.91 (0.71, 1.18)	0.87 (0.66, 1.14)
Charlson comorbidity index (z-transformed)	REF	0.92 (0.72, 1.18)	0.91 (0.70, 1.19)	0.90 (0.67, 1.19)	0.93 (0.68, 1.27)
CRS_S status (vs. never CRS_S)[c] Past CRS_S Current CRS_S	REF	 1.06 (0.51, 2.20) 0.79 (0.38, 1.64)	 1.04 (0.49, 2.19) 0.79 (0.37, 1.71)	 0.79 (0.34, 1.83) 1.06 (0.48, 2.34)	 0.75 (0.31, 1.80) 1.07 (0.46, 2.48)

***p-value < 0.001, **p-value < 0.01, *p-value < 0.05
Abbreviations: CRS_S = European Position Paper on Rhinosinusitis subjective symptoms definition for CRS classification
[a] Fixed measurement error associated with latent class membership; allowed interpretation of latent classes to be unchanged with addition of covariates.
[b] Based on responses to four questions, at baseline, from the ID Migraine questionnaire.
[c] CRS status determined using self-reported symptoms relevant to CRS_S at all observed time-points up to and including closest to time of CT scan; never CRS = never met CRS_S criteria over follow-up; past CRS = met CRS_S criteria at some point in lifetime or over follow-up, but did not meet criteria at time of CT scan; current CRS = met CRS_S criteria at time of CT scan.

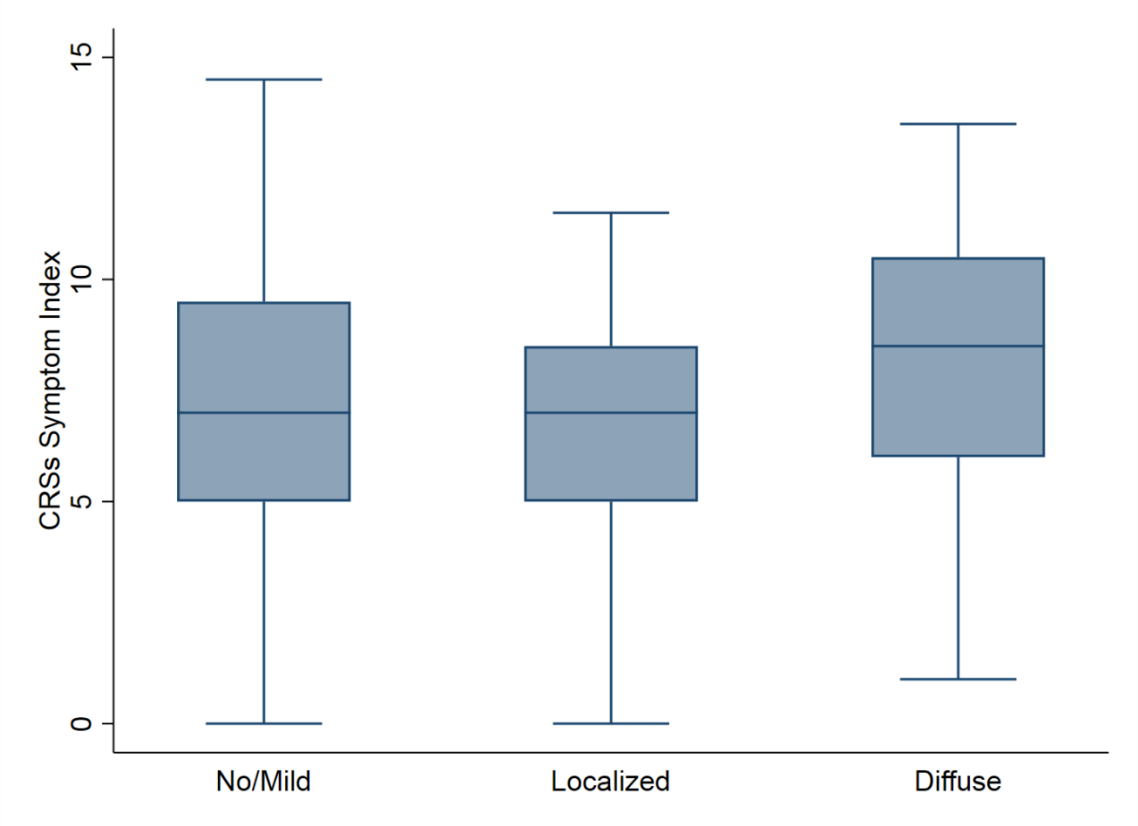


Figure 5.8.2. Box-and-whisker plot of CRS_S symptom index within latent classes. The symptom index was created by summing frequency scores (0 to 4 from never to all of the time) for four CRS symptoms groups. See Methods for additional details.

Table 5.8.5. Associations of six core CRS_S symptoms with selected covariates in a multivariate (multiple-outcome) ordered probit[a] model with three influential observations removed

Variables	NB	ND[b]	PND[c]	SL	FPN[d]	FPR[e]
Latent class (vs. no/mild)						
Localized	-0.06 (-0.28, 0.16)	0.11 (-0.17, 0.38)	0.12 (-0.15, 0.39)	-0.04 (-0.26, 0.19)	-0.13 (-0.35, 0.09)	-0.10 (-0.32, 0.11)
Diffuse	0.27 (0.01, 0.53)*	0.22 (-0.09, 0.53)	-0.07 (-0.38, 0.24)	0.37 (0.10, 0.63)**	0.07 (-0.19, 0.33)	0.08 (-0.18, 0.34)
Migraine headache status (vs. no)[f]	0.23 (0.03, 0.43)*	0.27 (0.02, 0.52)*	0.10 (-0.15, 0.35)	0.30 (0.10, 0.50)**	0.49 (0.29, 0.70)***	0.46 (0.25, 0.66)***
Latent class by migraine headache status interaction						
Localized		-0.56 (-1.00, -0.14)*	-0.62 (-1.05, -0.20)**			
Diffuse		-0.003 (-0.53, 0.52)	-0.07 (-0.38, 0.24)			

***p-value < 0.001, **p-value < 0.01, *p-value < 0.05;
Abbreviations: CRS_S = European Position Paper on Rhinosinusitis subjective symptoms definition for CRS classification
[a] Ordered probit regression yielded β-coefficients which represented a β-change in z-score of underlying outcome scale; all models adjusted for season, female sex, ASI, migraine status, and binary indicator for whether symptoms taken from questionnaire occurred > 90 days from time of CT scan.
[b] Additionally included ASI^2 and interactions for female sex by ASI and ASI^2.
[c] Additionally included self-reported physician diagnosis of hay fever, age, and interactions for female sex by ASI and by age.
[d] Additionally included age, age^2, Charlson comorbidity index, binary indicator for receipt of Medical Assistance, ASI^2, and interactions for female sex by ASI and ASI^2.
[e] Additionally included self-reported physician diagnosed hay fever, age, and age^2.
[f] Based on responses to four questions, at baseline, from the ID Migraine questionnaire.

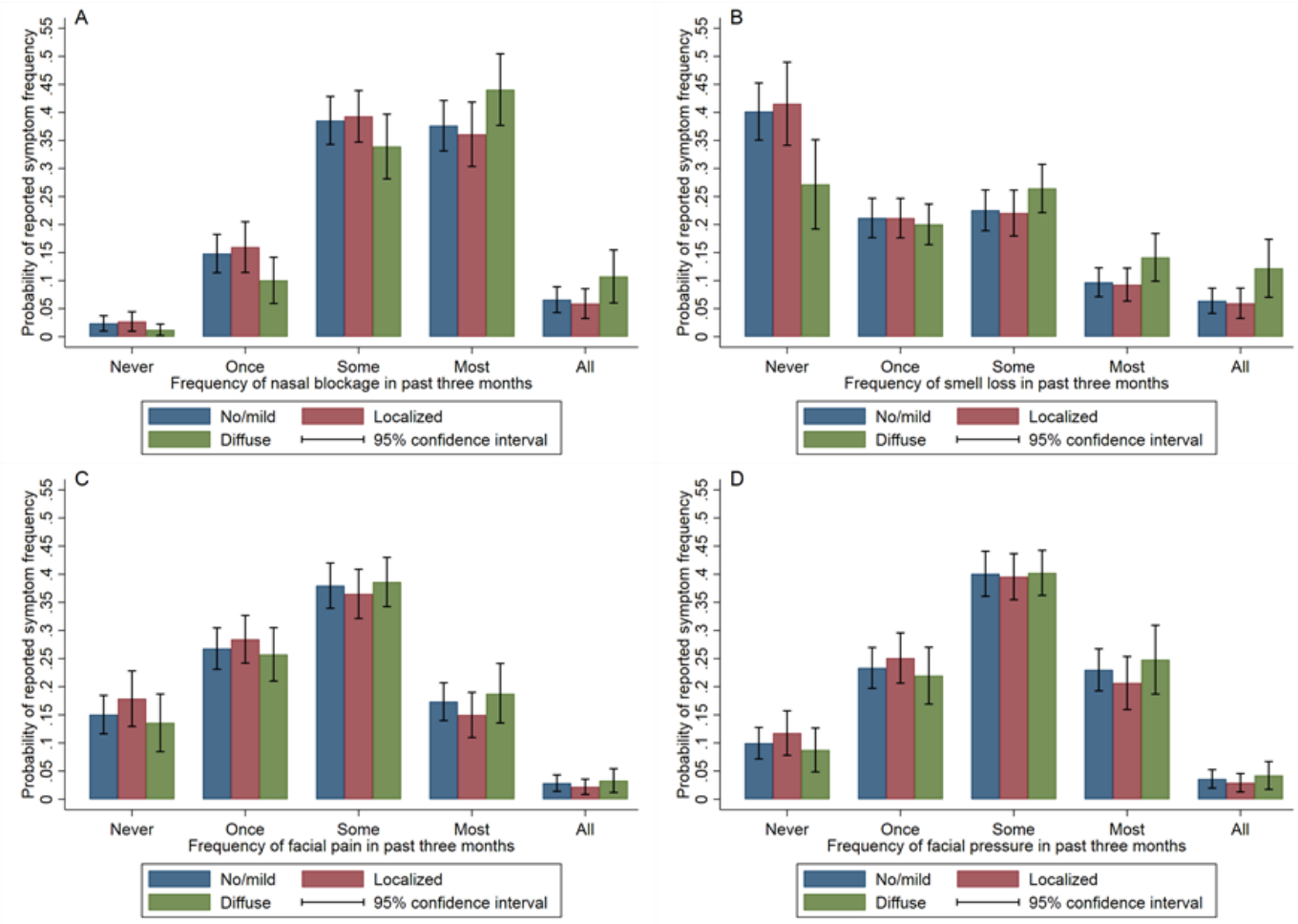


Figure 5.8.3. Marginal probabilities of self-reported symptoms at all frequency categories (in the past three months), by latent class. Estimates based on an adjusted multivariate ordered probit regression model. Nasal blockage (A), smell loss (B), facial pain (C), and facial pressure (D). Frequency categories were: never, once in a while (“once”), some of the time (“some”), most of the time (“most”), and all of the time (“all”).

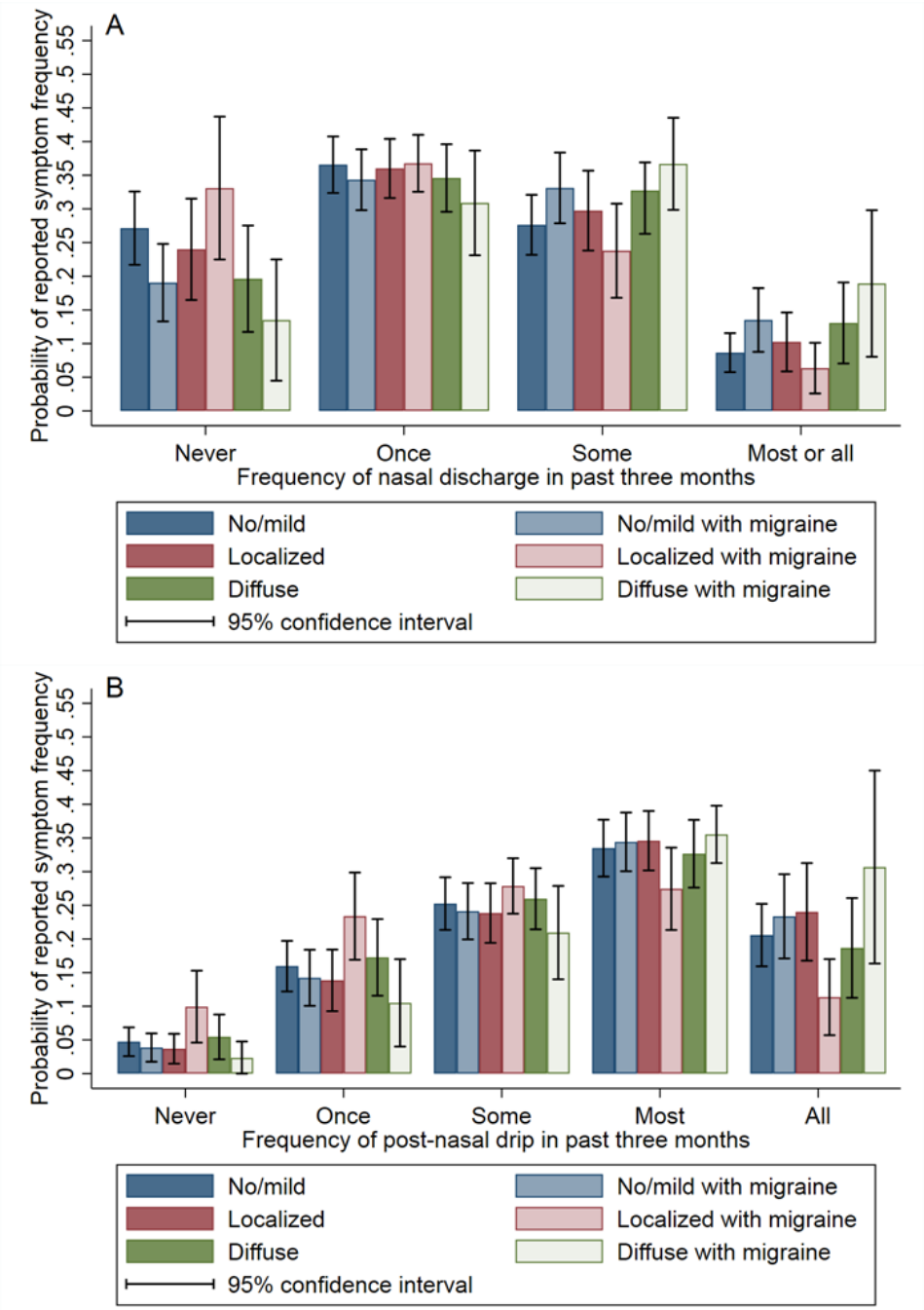


Figure 5.8.4. Marginal probabilities of self-reported symptoms at all frequency categories (in the past three months), by latent class and migraine status. Estimates based on an adjusted multivariate ordered probit regression model. Nasal discharge (A) and post-nasal drip (B). Frequency categories were: never, once in a while ("once"), some of the time ("some"), most of the time ("most"), and all of the time ("all"). The two highest frequency categories were combined for nasal discharge since there were only four observations in the highest category.

Chapter 6: Miscellaneous results: CFA and MIMIC model of CRS_S

6.0 Introduction

Chronic rhinosinusitis (CRS), is a prevalent and disabling condition characterized by inflammation of the paranasal sinuses.[1-4] Several consensus groups operationalize clinical CRS by objective evidence of inflammation (e.g., sinus computed tomography [CT] scan, endoscopy, magnetic resonance imaging [MRI]) and subjective nasal and sinus symptoms (NSS).[2-4] Given the difficulty in obtaining objective evidence of inflammation in epidemiologic studies, the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) has recommended using the subjective symptoms component as the criterion for classification with CRS (CRS_S).[2] CRS_S is defined by the presence of nasal blockage/congestion, anterior/posterior nasal discharge, smell loss, or facial pain/pressure; an individual must self-report two or more symptoms (one of which must be nasal blockage or discharge) lasting at least three months to be classified with current CRS_S.[2]

While CRS_S has been used in several epidemiologic studies,[1,5-7] no study has been done to confirm the construct validity of its operationalization. We have previously shown that the defining CRS symptoms – symptoms that could result from several overlapping conditions (e.g., CRS, asthma, allergic rhinitis, migraine headaches) – measure at least three different domains;[8] however, the various approaches to summing symptoms for CRS_S imply that the symptoms are equivalent and hence any underling symptom factor is unidimensional. Misclassification of symptoms for CRS could occur if symptom occurrence is truly multidimensional. Further, CRS_S assumes exchangeability of anterior nasal discharge with post-nasal drip (i.e. posterior nasal discharge) as well as facial pain with facial pressure. However, we have previously shown differential associations of radiologic inflammation (measured by sinus CT) patterns with these symptoms, suggesting they may not be fully exchangeable (**Chapter 5**). Additionally, facial pain is

commonly reported in several conditions, including tension headache, migraine headache, vascular headache (e.g., hemicrania continua, cluster headache, and paroxysmal hemicrania), and orodental pathologies[2]; but, it is uncommon in CRS,[9] especially when nasal polyps are present (i.e. CRSwNP),[10] and is usually only reported during onset of acute bacterial infection.[2] Therefore, it is possible that certain CRS_S symptoms may have different contexts (i.e. differential item functioning [DIF]), depending on an individual's comorbidities, which could lead to bias in classification with CRS_S.

Given the possible multidimensionality of CRS_S and DIF by comorbidities, we used self-reported NSS from a general population representative sample of individuals, across a broad spectrum of sinus disease, to answer the following questions:

1) Is CRS_S unidimensional or are multiple constructs identified by these six symptoms?
2) Are there sex and comorbidity differences with respect to the underlying construct(s)?
3) Is there DIF by sex and comorbidity status for any of the CRS_S symptoms?

6.1 Materials and methods

6.1.1 Study overview and sample

The details on the study design and sample have been published elsewhere.[1,7,8] Briefly, out of 200,769 individuals from the electronic health record (EHR) of Geisinger, a large healthcare system in central and northeastern Pennsylvania, 23,700 were selected to participate in a longitudinal epidemiologic study of CRS, NSS, and related symptoms and conditions based on *International Classification of Diseases* (ICD-9) and *Current Procedural Terminology* codes. Of the 23,700 selected, 7847 returned a baseline questionnaire which included (among other components) the six questions comprising CRS_S and were subsequently followed through 16 months, with four questionnaires provided during this follow-up period (all of which also included the CRS_S relevant

questions). After excluding individuals with missed questionnaires and excessive item-level missingness (i.e. greater than five questions), 3535 individuals remained for subsequent analyses.

6.1.2 CRS_S symptoms

CRS_S symptoms, including nasal blockage/congestion, anterior nasal discharge, post-nasal drip, smell loss, facial pain, and facial pressure were self-reported from all individuals at each questionnaire. The frequency of these symptoms in the past three months were reported using a five-point Likert scale (0 = never, 1 = once in a while, 2 = some of the time, 3 = most of the time, and 4 = all of the time).

6.1.3 Selected covariates

We chose sex, anxiety sensitivity index (ASI), and self-reported physician diagnoses of asthma, hay fever, and migraine as covariates in this study. We selected sex and the comorbidities as covariates given their prior associations with current CRS_S in a separate study.[1] We included ASI, a measure of a person's fear of anxiety-related physical symptoms,[11] as we hypothesized that individuals with greater ASI may either be more aware of their symptoms or overreport symptoms, thereby leading to differential measurement of these symptoms.

6.1.4 Confirmatory factor and multiple indicator-multiple cause analyses

Confirmatory factor analysis (CFA) is a measurement modeling approach in which dimensionality of an underlying construct is theoretically or empirically known (one of the key features distinguishing it from exploratory factor analysis [EFA]).[12] CRS_S arguably assumes a unidimensional construct based on responses to four symptom groups, therefore we set to use a CFA framework to statistically test this assumption. While CRS_S assumes exchangeability of anterior nasal discharge with post-nasal drip and facial pain with facial pressure, we included these as separate questions on the questionnaires. However, to be more congruent with rationale imposed by CRS_S

operationalization, we included *a priori* paths between these pairs of symptoms to allow for residual correlation among these indicators, since conditional independence is an assumption in both EFA and CFA.[12,13] This basic model became our base model.

We tested for differences in means of the underlying factor identified in our base model by introducing indirect effects (i.e. paths from covariates to latent factor) of selected covariates. This model is known as the multiple indicator-multiple cause (MIMIC) model or sometimes called a CFA with covariates.[14] We further assessed for DIF by including paths from selected covariates to CRS_S symptoms. These direct effects were guided by modification indices (e.g., Lagrange multipliers[15]) and added one at a time, beginning with the most significant parameter.

6.1.5 Statistical analysis

CFA and MIMIC models were estimated in Mplus v.8.1 (Muthén & Muthén, Los Angeles, CA) using robust weighted least squares and fixing the factor loading for nasal blockage to one for model identification. Model fit was assessed by root mean square error of approximation (RMSEA),[16,17] comparative fit index (CFI),[18] Tucker Lewis index (TLI),[19] and standardized root mean square residual (SRMR).[20] Parameter estimates are presented in unstandardized form in path diagrams and standardized form in **Table 6.2.2.2**. While our primary analyses were completed using baseline questionnaire responses, we reassessed all models using responses from the 16-month follow-up questionnaire, as a sensitivity analysis.

6.2 Results

6.2.1 Characteristics of sample

Descriptive information on this sample can be found in the previously published Appendix (Cole et al. 2018).[8] Briefly, males constituted 37.8% of the sample; the mean age was 57.5 years; the median ASI score was 10; and 24.5%, 47.0%, and 28.7% of

subjects self-reported physician diagnosis of asthma, hay fever, or migraine, respectively.

6.2.2 CFA model with no covariates

Our base CFA model fit the data well with a RMSEA of 0.035, CFI and TLI values of 1.00 and 0.999 (respectively), and SRMR of 0.007 (**Table 6.2.2.1**). All six CRS_S symptoms significantly loaded onto the factor (unstandardized parameters; **Figure 6.2.2.1**). While the estimate for the correlation between facial pain and facial pressure was not significant, we retained this in the model since we specified it *a priori* as a key component of the model.

Table 6.2.2.1. Selected fit metric for all CFA models, by questionnaire (baseline or 16-month follow-up)

	Base model		Indirect effects added		Direct effects added	
Fit metric	Baseline	16-month	Baseline	16-month	Baseline	16-month
RMSEA[a]	0.035	0.019	0.045	0.047	0.021	0.023
CFI[b]	1.00	1.00	0.996	0.996	0.999	0.999
TLI[c]	0.99	1.00	0.995	0.995	0.999	0.999
SRMR[d]	0.007	0.006	0.032	0.038	0.009	0.012

Abbreviations: CFI = comparative fit index; RMSEA = root mean square error of approximation; SRMR = standardized root mean square error; TLI = Tucker Lewis index

[a] value < 0.08 generally indicates good model fit
[b] value ≥ 0.95 generally indicates good model fit
[c] value ≥ 0.90 generally indicates good model fit
[d] value < 0.08 generally indicates good model fit

As a sensitivity analysis, we estimated the CFA model using responses to the 16-month follow-up questionnaire, to determine whether model results were replicable or

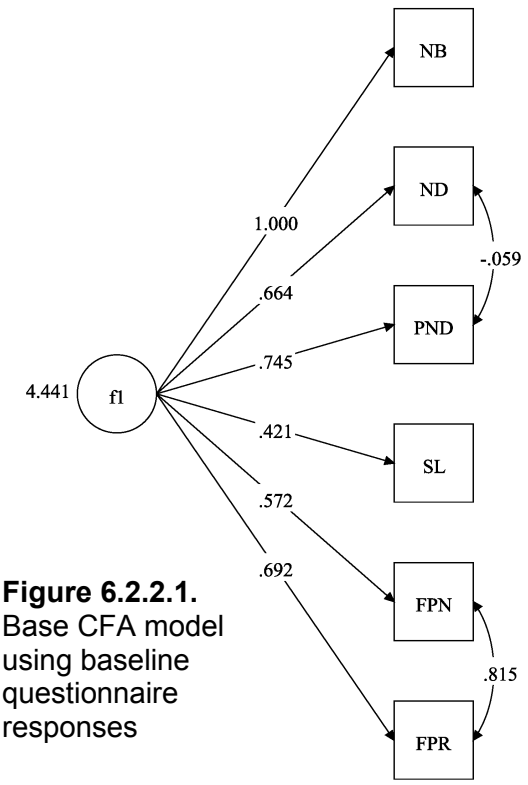


Figure 6.2.2.1. Base CFA model using baseline questionnaire responses

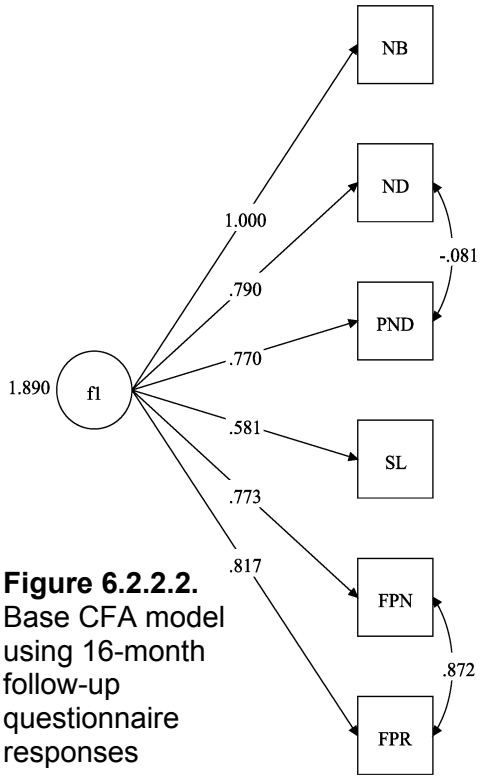


Figure 6.2.2.2. Base CFA model using 16-month follow-up questionnaire responses

spurious. Absolute measures of model fit (**Table 6.2.2.1**) and factor loadings (unstandardized parameters; **Figure 6.2.2.2**) were comparable in the 16-month CFA model to those of the baseline model (**Table 6.2.2.2**).

Table 6.2.2.2. Standardized factor loadings and indirect and direct effects of covariates

	Base model		Indirect effects added		Direct effects added	
Factor item	Baseline	16-month	Baseline	16-month	Baseline	16-month
Nasal blockage	0.90	0.81	0.91	0.82	0.91	0.82
Nasal discharge	0.81	0.74	0.82	0.74	0.83	0.76
Post-nasal drip	0.84	0.73	0.84	0.72	0.85	0.72
Smell loss	0.66	0.62	0.67	0.64	0.67	0.64
Facial pain	0.77	0.73	0.78	0.74	0.74	0.70
Facial pressure	0.83	0.75	0.83	0.76	0.81	0.73
Covariate effects, indirect						
Female sex			0.09	0.04	0.13	0.12
Asthma			0.20	0.14	0.20	0.14
Hay fever			0.39	0.42	0.41	0.45
Migraine headache			0.36	0.41	0.26	0.30
Anxiety sensitivity index (ASI, z-transformed)			0.16	0.23	0.15	0.22
Covariate effects, direct						
Nasal blockage						
Female sex					-0.15	-0.19
Nasal discharge						
Female sex					-0.14	-0.21
Hay fever					-0.09	-0.13
Smell loss						
Female sex					-0.14	-0.19
Facial pain						
Female sex					0.12	0.12
Migraine headache					0.26	0.22
ASI					0.03	0.05
Facial pressure						
Female sex					0.07	0.09
Migraine headache					0.22	0.22

6.2.3 CFA model with covariates

We next entered sex, ASI, and self-reported physician diagnoses of asthma, hay fever, and migraine into the base model as indirect effects, i.e. allowed to associate with the latent variable, but not the six CRSs

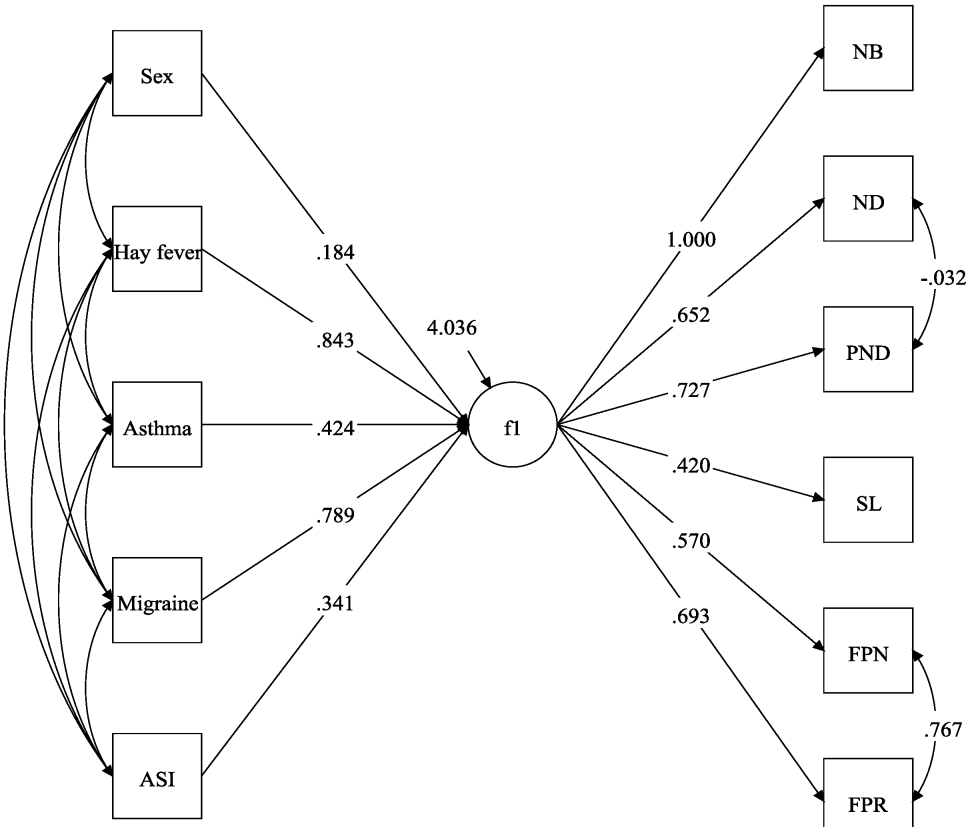


Figure 6.2.3.1. CFA model with indirect effects of selected covariates, using baseline questionnaire responses. ASI = anxiety sensitivity index; FPN = facial pain; FPR = facial pressure; NB = nasal blockage; ND = nasal discharge (anterior); PND = post-nasal drip; SL = smell loss

symptoms directly (unstandardized parameters; **Figure 6.2.3.1**). Model fit was still acceptable with a RMSEA of 0.045, CFI and TLI of 0.996 and 0.995 (respectively), and SRMR of 0.032. All symptoms again significantly loaded onto the latent factor and all covariates were significantly associated with the factor as well (**Table 6.2.2.2**). These significant indirect associations indicated differences in means of the underlying factor by sex, ASI, or self-reported physician diagnoses. In absolute terms, self-reported physician diagnosis of migraine and hay fever as well as higher ASI were most associated with the latent factor.

In the CFA model using responses from the 16-month questionnaire, model fit was comparable to that of the baseline questionnaire model (**Table 6.2.2.1**), although sex no longer had a significant association with the latent factor (unstandardized parameters; **Figure 6.2.3.2; Table 6.2.2.2**).

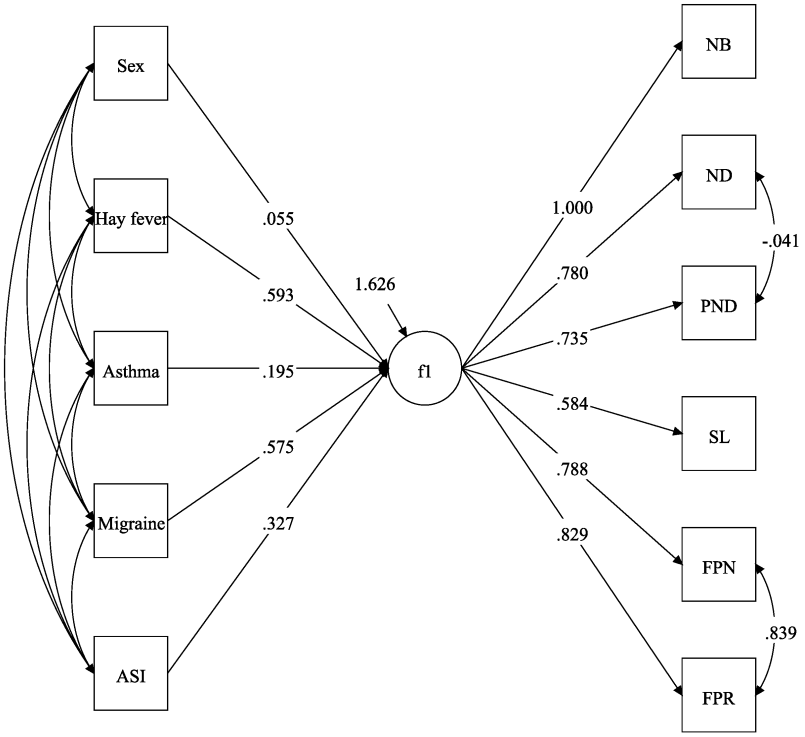


Figure 6.2.3.2. CFA model with indirect effects of selected covariates, using 16-month follow-up questionnaire responses. ASI = anxiety sensitivity index; FPN = facial pain; FPR = facial pressure; NB = nasal blockage; ND = nasal discharge (anterior); PND = post-nasal drip; SL = smell loss

Lastly, to determine whether there was any DIF present vis-à-vis the selected covariates, we entered direct effects for these covariates, i.e. opened paths from the covariates to the CRS_S symptoms directly (unstandardized parameters; **Figure 6.2.3.3**). All covariates were again positively associated with the latent factor while DIF by sex, self-reported physician diagnosis of migraine and hay fever, and ASI were observed (**Table 6.2.2.2**). Considering the potential DIF, female sex was consistently associated with nasal blockage, anterior nasal discharge, smell loss, facial pain, and facial pressure; however, the direction of associations were dependent on the symptom. Female sex was negatively associated with nasal blockage, anterior nasal discharge, and smell loss, and positively associated with facial pain and facial pressure. Self-reported physician diagnosis of hay fever was

negatively associated with anterior nasal discharge while self-reported physician diagnosis of migraine was consistently positively associated with facial pain and facial pressure. Lastly, ASI was positively associated with facial pain only (unstandardized parameters; **Figure 6.2.3.3**).

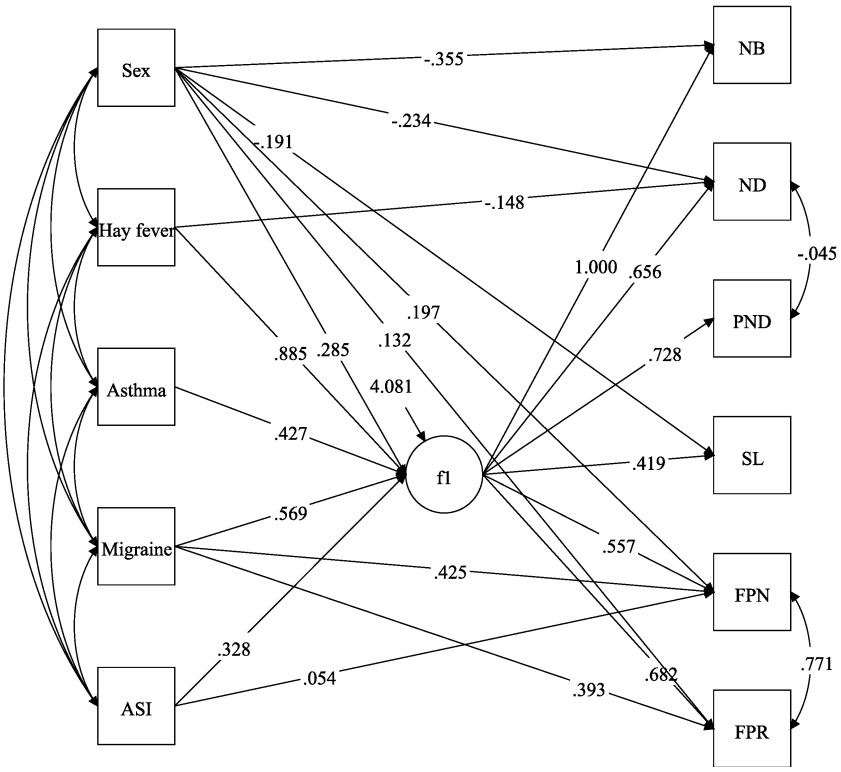
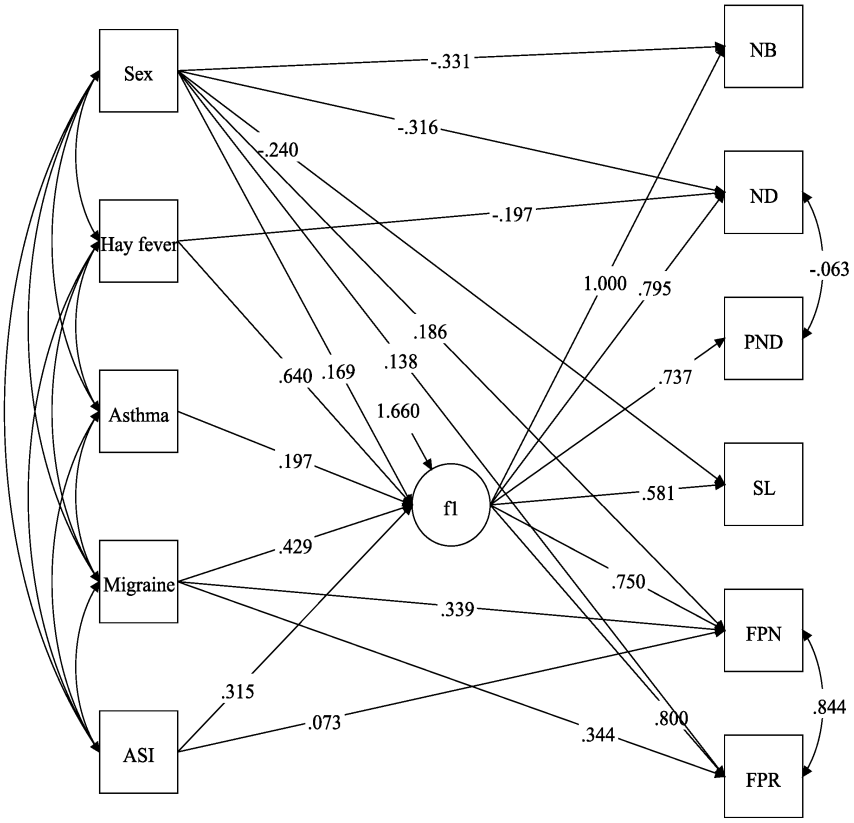


Figure 6.2.3.3. CFA model with indirect and direct effects of selected covariates, using 16-month follow-up questionnaire responses. ASI = anxiety sensitivity index; FPN = facial pain; FPR = facial pressure; NB = nasal blockage; ND = nasal discharge (anterior); PND = post-nasal drip; SL = smell loss

We reassessed this CFA model with responses from the 16-month questionnaire.



Model fit (**Table 6.2.2.1**), factor loadings, indirect effects, and direct effects were all comparable to those estimated in the baseline questionnaire model (**Figure 6.2.3.4; Table 6.2.2.2**).

Figure 6.2.3.4. CFA model with indirect and direct effects of selected covariates, using 16-month follow-up questionnaire responses. ASI = anxiety sensitivity index; FPN = facial pain; FPR = facial pressure; NB = nasal blockage; ND = nasal discharge (anterior); PND = post-nasal drip; SL = smell loss

6.3 Discussion

In this study, we used a general population representative sample of individuals across a broad spectrum of sinus disease, to address the following questions:

1) Is CRS_S unidimensional?
2) Are there differences in association with CRS_S by sex, ASI, and self-reported physician diagnoses?
3) Is uniform DIF present in CRS_S by the aforementioned covariates?

To our knowledge, this is the first study to address the above questions, despite the common use of CRS_S in epidemiologic studies.[1,2,5-7]

CRS_S is comprised of four major symptoms groups (six individual symptoms), including nasal blockage, anterior nasal discharge/post-nasal drip, smell loss, and facial pain/pressure, with nasal blockage and anterior/posterior nasal discharge serving as anchoring symptoms (i.e. at least one is required).[2] While this operationalization is suggestive of a unidimensional construct, we have recently shown that these symptoms may be represented by as many as three latent constructs, when considered with additional NSS questions related to severity and bother, and while also including asthma, allergy, and constitutional symptoms in the model.[8] Our base CFA models found a single factor model fit the data appropriately, suggesting that perhaps these four symptom groups do measure a single underlying construct, when only considered together (and not with additional NSS). Though, with only six indicators our ability to detect additional constructs is limited.

It is important to note the insignificant correlation between anterior nasal discharge and post-nasal drip in all models tested. CRS_S currently assumes that these symptoms are interchangeable, the same of which is true for facial pain and facial pressure; however, a lack of residual correlation between these symptoms may suggest that they

are not necessarily exchangeable with one another and should be considered as separate contributions to the operationalization.

In the CFA models with indirect effects, female sex was positively associated with the latent factor as were ASI and self-reported physician diagnoses of asthma, hay fever, and migraine. These observations are congruent with those of a prior study of CRS_S, though associations with ASI were not reported by the authors.[1]

Considering our CFA models that allowed indirect and direct effects of covariates, we observed several of the CRS_S symptoms to have DIF by one or more of the covariates. However, considering that these questions did not have any apparent difficult wording or phrasing, we do not consider the observed DIF associations to be "adverse," but rather "benign."[21] Simply put, benign DIF occurs when a question identifies a different dimension in the construct that is not directly measured or manifests differently across subgroups of individuals. On the other hand, adverse DIF is essentially artifactual measurement error derived from the generation of the indicators used to measure the underlying construct.[21] Females, while having a greater association with the underlying factor than males, exhibited systematic underreporting of nasal blockage, anterior nasal discharge, and smell loss while overreporting facial pain and facial pressure. This sex-dependent item functioning has important implications for the validity of CRS_S when applied uniformly to males and females. If certain types of symptoms (e.g. facial vs. nasal) are reported differentially by the basis of sex, then it is possible that CRS_S may not have the same context across the sexes.

ASI, a measure of a person's fear of anxiety-related physical sensations (believing these sensations to be harmful),[11] was positively associated with facial pain, meaning individuals with greater ASI were more likely to overreport this symptom than those with less ASI. While we have no explanation for this observed association, it is possible that

individuals with greater ASI have a lower pain threshold than those with lower ASI, thereby being more likely to report pain, even if biological inflammation resulting in that pain is comparable.

We observed a negative association of self-reported physician diagnosis of hay fever with anterior nasal discharge, implying a systematic underreporting of this symptom among individuals with hay fever, compared to those without. This is as expected since our question pertaining to anterior nasal discharge asked about purulent (e.g., yellow or green in color) discharge specifically, which is not a common symptom of hay fever; mucous produced in response to allergens is usually clear and thin compared to that produced by infection.[22,23]

Lastly, self-reported physician diagnosis of migraine headaches was positively associated with facial pain and facial pressure. This was as hypothesized considering our prior associations of CRS_S with migraine headache, especially among individuals reporting these facial symptoms.[1] While there are several explanations for this, the most likely is that these symptoms are manifested in a multitude of overlapping conditions, including CRS and migraine headache[2]; therefore, it is possible that these symptoms are really measuring a construct representing migraine headache when asked among individuals with this diagnosis, instead of the intended construct (i.e. CRS).

In this study, we observed several instances of DIF in a CRS_S construct by sex and various comorbidities. While we do not believe these are related to inappropriate question formation (i.e. adverse DIF), they do highlight the difficulties in creating a definition of symptom-based CRS, especially when there are likely pathogenic differences by sex and overlapping conditions.

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Chapter 7: Discussion

7.0 Summary of findings

The aims of this dissertation were to: comparatively assess multiple definitions of acute exacerbations of nasal and sinus symptoms (AENSS) and describe their respective risk factors; estimate the workplace impacts of nasal and sinus symptoms (NSS) and related symptoms and diagnoses; and develop a new approach to categorization of radiologic inflammation in chronic rhinosinusitis (CRS). As we became immersed in CRS research, we realized that the measurement of CRS symptoms, AENSS, and radiologic inflammation were all problematic. As such, the research presented in this dissertation became mainly about measurement of multidimensional constructs.

In our first study[1] (**Chapter 3**), we directly addressed a call-to-action from the International Consensus on Allergy and Rhinosinusitis, wherein there was an expressed need for comparative assessments of several definitions for the acute exacerbations of CRS, especially in general population samples.[2] We developed several operationalizations of NSS exacerbations, with varying degrees of specificity, including one related to antibiotic and oral corticosteroid use for worsened NSS (AENSS-Med); timing of symptoms (AENSS-Sx); and timing of symptoms with the requirement that one worsened symptom was mucopurulence (AENSS-Sx-Pur). We declined to refer to these definitions as AECRS, since we did not have objective evidence of inflammation and therefore could not classify individuals with clinical CRS (CRS_C), only subjective symptoms CRS (epidemiologic definition; CRS_S).

We found that NSS and AENSS were common in the general population, but exacerbations occurred more frequently in those with long-term CRS_S status.[1] Further, we observed a seasonal association with all AENSS definitions, though most pronounced in AENSS-Med. We argued that this was due to increased presumptive

treatment for viral or bacterial infections common during winter and increased allergen exposures in the spring.

Comparing the respective risk factors for each definition of exacerbation, we found several to be consistent across all definitions, including CRS_S status, asthma (symptoms at baseline), self-reported physician diagnosed hay fever, and migraine headache.[1] These risk factors further support the concept of the unified airway disease model.[3] Ultimately, we reasoned AENSS-Sx-Pur to be the definition least influenced by medical-seeking and -prescribing behaviors and was more specific than either AENSS-Med or AENSS-Sx.

In our second study[4] (**Chapter 4**), we provided the first general population-based analysis of the workplace impacts of NSS and related symptoms. We also attempted to disentangle these relations from those of condition status (i.e. the presence and severity of current symptoms) and diagnosis, in an effort to better understand whether symptoms or other aspects of a condition were the major drivers of workplace lost productive time (LPT).

We took a novel approach to assessing symptoms and their associations with LPT, among individuals across the broad spectrum of sinus disease, by using symptom-based factor scores from exploratory factor analysis (EFA) models we developed in a separate analysis and subsequent publication from the same longitudinal study from which my dissertation data were derived.[5] By doing so, we could better understand which sets of symptoms were most associated with to declines in workplace productivity. We found symptom factors relevant to nasal blockage and discharge; facial pain and pressure; and asthma and constitutional symptoms were most associated with increased LPT, after controlling for several confounders (e.g., sex, age, anxiety sensitivity) and condition

statuses (e.g., migraine headache, self-reported physician diagnosis of asthma, self-reported physician diagnosis of hay fever, CRS_S).[4]

While facial pain had previously been associated with increased workplace presenteeism, in a prior study,[6] something we corroborated, it is interesting that facial pain (but not facial pressure) has been negatively predictive of being classified with CRS in clinical settings.[7] This further demonstrates the complexity in defining CRS based solely on symptoms, especially when they overlap with several other conditions. Additionally, this iterates the possibility that individuals with classifiable disease (i.e. meets CRS_S criteria) may not necessarily have the most severe symptoms or negative outcomes.

In a patient-centered care setting,[8] these findings can be used to better educate patients and bring awareness to how these symptom groups can adversely impact daily functioning. Better management of these particular symptoms may also lead to improved workplace productivity.

Finally, our last study (**Chapter 5**) sought to extend the issue of measurement of CRS_C components (i.e. CRS_S and objective evidence-based CRS [CRS_O]), which we began in our exploratory factor analyses of NSS and related symptoms (identifying three constructs relevant to CRS instead of the one theoretically implied by CRS_S),[5] by turning our focus to CRS_O. Consensus groups,[2,9,10] clinicians,[11] and researchers[12] have all used a single-score approach to quantify radiologic inflammation in sinus disease, obtained by sinus CT. We first compared a common scoring approach (Lund-Mackay [LM]) and its intended improvement (modified Lund-Mackay [mLM]) by using EFA models to determine whether both measured the same underlying constructs. Both approaches identified one underlying construct, i.e. sinus inflammation, with no noticeable differences between them. Further, we included nasal cavity opacification as part of the

scoring process to determine if any additional information could be gleaned by its inclusion, since nasal polyposis (identifiable as nasal cavity opacification) is a major component of one phenotype of CRS (CRS with nasal polyps [CRSwNP]).[9] However, we saw no additional constructs emerge nor did factor loadings (i.e. associations of sinus locations with underlying construct) change by including nasal cavity opacification; though, we were likely underpowered to detect differences imparted by its inclusion.

We subsequently used a latent class approach to determine whether patterns of sinus opacification could discern mutually exclusive subgroups of individuals. We hypothesized that subgroups of individuals may opacify in different locations and patterns, which would be contrary to a single-score approach, which assumes all locations are exchangeable (i.e. opacification is random or sporadic). We identified three latent subgroups of individuals comprising a no/mild opacification class; localized opacification class, predominantly in the maxillary sinus; and a diffuse opacification class, almost always in the anterior ethmoid and always involving two or more sinus locations. Interestingly, these opacification patterns shared similarities with known otorhinological drainage routes.[13] Additionally, we found differences by sex in the proportion of persons across these three classes, with males more likely to be in the diffuse class, compared to females. Also, there was a tendency for increased risk of being in the localized or diffuse classes if an individual self-reported physician diagnosis of asthma or hay fever and met symptom criteria for migraine headaches.

Another novelty of our study was the appreciation for causal directionality in the relation of radiologic inflammation with symptoms. While prior studies have assessed the two in the wrong causal direction (i.e. using symptoms as the independent variables to predict inflammation as the dependent variable, when the actual causal direction is that inflammation causes symptoms),[12,14-16] we performed a series of regression models to

evaluate the associations of opacification latent classes with self-reported CRS_S symptoms. By doing so, we observed the diffuse class was associated with nasal blockage and smell loss, but no other symptoms, while the localized class had no increased probability of CRS_S symptoms, compared to the no/mild class.

While future studies are needed to elucidate the clinical relevance of these latent classes, our study suggests that a single-score approach to quantifying radiologic inflammation in sinus disease is incorrect; rather, location and patterns, as well as possibly severity, of sinus opacification should be considered.

7.1 General population vs. tertiary care samples

In all of our studies, we used a general population-based sample with individuals representing the broad spectrum of sinus disease. Nearly all prior studies of CRS have selected individuals from tertiary referral settings, were generally pre-surgical, and likely represent the most severe end of the disease spectrum. As such, our understanding of CRS has been limited to what was observed in this subpopulation, e.g., surgical candidates are often symptomatic (initially leading them to seek care) and have extensive radiologic inflammation.[9,17-19] However, our CT study sample (**Chapter 5**) shows a more heterogeneous mix of symptoms and radiologic inflammation. We observed asymptomatic individuals across the entire LM score range and highly symptomatic individuals with no measurable opacification. Further, our average LM score was much lower than those reported in tertiary care studies.[17,20-22] The shift in LM scores towards the lower end of the distribution was expected considering, again, that we selected individuals from a general population sample and selection was independent of radiologic inflammation (i.e. extent of sinus opacification was not known prior to study).

While studies of tertiary referral patients are important for understanding the late-stage disease process and its implications, they are not suitable for studies earlier in disease progression. As such, general population samples with individuals across the disease spectrum are necessary, especially if studies aim to understand the intervenable points during pathogenesis and how varied etiologic agents relate to disease trajectory.

7.2 Future research directions and implications for clinical practice and epidemiologic research

In this section, we discuss the future directions for CRS research in the context of our recent findings, their limitations, and what additional studies will be needed to address them. Specifically, we discuss the need for replication in our own source population; replication in other study populations; longitudinal studies to provide context to our three sinus opacification latent classes; longitudinal studies to evaluate disease progression; and detail necessary studies to build upon our findings relevant to measurement of CRS_S and CRS_O, with the aim of improving the definition for CRS_C.

7.2.1 Replication in source population

In our studies, we selected individuals from the electronic health record (EHR) of Geisinger (a large healthcare system in predominantly northeastern and central Pennsylvania) to participate in our longitudinal, questionnaire-based, epidemiologic study of CRS. To validate our findings, it would be advisable to replicate our analyses in a new subset of individuals from this source population, following the same sampling strategy.[23] This internal replication is useful in determining the extent to which our previous findings were dependent on subject selection and participation.

7.2.2 Replication in other study populations

While our study sample was representative of the general population *for the area*, it is not representative of the general U.S. population. Replication in other U.S. geographies, especially those with greater racial/ethnic diversity, will be paramount to better understanding the generalizability of our findings. Further, we previously (**Chapter 1**)

highlighted the international geographic variation in prevalence and phenotypic and endotypic profiles of CRS. For example, Asian populations tend to display a T-helper 1/T-helper 17 (Th1/Th17) mixed inflammatory profile with CRSwNP and Th2 with CRSsNP (CRS without nasal polyps), whereas the converse is generally true for studied populations in the U.S. and Canada.[9,24-26] Therefore, it would be advisable to replicate our studies in not just other U.S. populations, but other countries, too.

Considering our analyses presented in **Chapter 5**, the latent class approach to categorization of radiologic inflammation should be replicated in other U.S. general population-based samples (i.e. not tertiary referral settings) to determine the external validity of our original findings, while replication in general population samples from other countries would elucidate its transportability.

7.2.3 Longitudinal studies: context of our latent classes

While our latent classes share similarities with known otorhinological drainage routes,[13] we have limited context to which we can understand the full clinical relevance of these subgroups. Further, the estimated latent classes may be sensitive to the range of individuals selected for participation in the study. While we selected individuals from the broad spectrum of disease, we may, for example, be able to detect subgroups of our diffuse opacification class if we assessed opacification patterns among a sample of the most severely diseased individuals only. This could potentially be more imperative to identification of discrete endotypes of CRS, considering the latent classes obtained in our general population sample may not all necessarily be CRS specific.

Without longitudinal (i.e. repeated) sinus CT measures, we cannot determine whether the three classes represent endotypes of CRS, different stages along the same disease process (i.e. different stages of severity), different conditions along the same broad process (i.e. acute rhinosinusitis [ARS] to CRS), or discrete pathologies (e.g., migraine headache and CRS). If these latent classes truly represented phases along a single

progressive disease process, we would have likely expected the posterior probabilities of sinus opacification in all six locations (**Chapter 5**) to increase systematically as disease severity (i.e. extent of sinus opacification) increased, too.[27] While we did not necessarily observe this progressive relation with out latent classes in the cross-sectional setting, a prior study of sinus CT scans among individuals presenting to primary care settings with ARS may give further insight to our localized latent class. [28] In that study, maxillary sinus opacification was more associated with ARS than any other sinus location,[28] a finding which corroborated the first study of sinus opacification in the common cold (e.g., ARS).[29] Given our localized latent class was driven primarily by isolated maxillary sinus opacification, it is possible that this latent class represents an ARS-dominant subgroup, while our diffuse latent class represents a CRS-dominant subgroup.

7.2.4 Longitudinal studies to assess disease progression and identify endotypes of CRS

We previously discussed a framework for rhinosinusitis (**Chapter 1**) in which a subset of individuals with ARS transition into CRS and either remit or persist over time.[30] Using a comparable sampling approach to that used in our studies – one in which a general population sample with individuals across the entire spectrum of disease is selected – our latent class approach could be extended to determine whether such a disease progression is plausible, given observed sinus opacification patterns. As mentioned above, different radiologic inflammation patterns could represent stages along a common disease continuum, discrete pathologies (i.e. representing different diseases), or different endotypes of the same disease state.

Previous studies of CRS_{ICD} (CRS classified by ICD codes) have suggested that individuals with CRS_{ICD} were more likely to have had a history of ARS_{ICD}[31]; therefore, it is plausible that some individuals with ARS, especially recurrent ARS (RARS), would transition into frank CRS.[30] Ideally, future studies would enroll individuals across the disease spectrum to participate in a longitudinal study of NSS and sinus CT scans, with

the primary goal of identifying transition from an asymptomatic state to ARS (possibly RARS) and eventually CRS. Formally, this could be done using a latent transition analysis (LTA) approach in which probability of transitioning from one latent class to another, over time, is directly estimated.[32] If individuals were most likely to stay within their original latent classes, then this would be evidence against disease progression and for discrete diseases or pathologies.

However, it is yet unclear as to the latency period for transitioning from acute to chronic sinus disease. Therefore, designing a prospective study of this sort would be difficult and expensive to sustain. Given the wealth of available longitudinal information provided by the EHR of Geisinger (which has had an EHR since 2001), a retrospective EHR study seems highly amenable to address research questions related to disease progression (over a possibly long period of time).

7.2.4.1 *Using biomarkers to identify type of progression*

Biomarkers including cytokines (e.g., chemokines, interferons, growth factors), antibodies, and hormones as well as microbiology should be evaluated within individuals comprising our estimated latent classes and in future longitudinal studies of CRS and possible disease progression as well as natural history. If disease progression is evidenced, this could be a progression along a narrow (i.e. early CRS to late CRS) or broad (i.e. ARS to recurrent ARS to CRS) continuum. To differentiate between these two possibilities, the characterization of the inflammatory profiles, NSS, and microbiology would be crucial. For example, it has been suggested that microbiology of ARS differs from those with CRS,[30] and therefore microbiology along with reported NSS (including frequency, duration, and severity) could aid differentiation.

7.2.4.2 *Using biomarkers to identify endotypes of CRS*

While biomarkers of inflammation would be useful in differentiating narrow or broad progression of disease, they would also be paramount to identifying endotypes of sinus

disease. For example, a prior study of CRS_C collected 14 inflammatory biomarkers from tissue samples of participants undergoing sinus surgery, finding 10 clusters (i.e. endotypes) represented by these individuals.[33] However, no prior studies have assessed inflammatory biomarkers in relation to disease progression (either from asymptomatic to ARS to CRS or from early-stage to late-stage CRS). Similarly, no prior studies have assessed differences in subsequent risks (e.g., worse prognoses, risk for subsequent morbidity, worse quality of life, workplace impacts) by inflammatory endotype.

We could leverage our CT scans and other data from **Chapter 5** to prospectively collect inflammatory biomarkers by readily accessible samples (e.g., nasal lavage fluid) and also perform additional CT scans, over follow-up. We could then use formal measurement models (e.g. latent profile analysis) to identify latent endotypes of inflammation, assess how these endotypes change over time (e.g., LTA), and how sinus opacification patterns relate to these endotypes (e.g., latent class regression).

7.2.5 CRS_C redefined

In our prior analysis using EFA, we identified as many as three CRS-relevant latent constructs measured by a set of 37 NSS and related symptoms.[5] This would imply that CRS_S, which theoretically measures one construct, is inappropriate given its encapsulation of several NSS domains. Further, our study of radiologic inflammation (**Chapter 5**) would suggest that the current approach to quantifying radiologic inflammation (and therefore operationalization of CRS_O) is also incorrect, with location and patterns of opacification being important considerations that are currently not incorporated. Therefore, an improved operationalization of CRS_C must contend with the multidimensionality of NSS commonly used in CRS_S as well as the need to incorporate location and patterns of sinus opacification in CRS_O.

One possibility is to extend these two components into a single structural equation modeling framework, wherein NSS factor scores are regressed on latent classes, to

determine whether any NSS factor or factors are predicted by radiologic inflammation patterns. Or, perhaps an approach more parallel to reality in which clusters of NSS (e.g., latent classes) are regressed on radiologic inflammation latent classes is warranted. Considering clustering of NSS may occur differentially in those with differing patterns of opacification, this approach would overcome limitations of the former, in which NSS factors are entered into latent class regression models as separate covariates (potentially missing complex interactions among the NSS factors).

However, the above approach may again only identify individuals with late-stage CRS. Therefore, multiple definitions of CRS may be necessary. For example, separate operationalizations could be used to identify individuals with early-, intermediate-, and late-stage disease, especially if future studies determine NSS to vary across the disease course (not just in severity, but in terms of which symptoms are reported).

7.2.5.1 *Implication for medical treatment and intervention*

If disease progression is observed, then it may be possible to intervene earlier in the process to prevent individuals from transitioning into more severe disease states (e.g., frank CRS). One approach would involve the use of endotyping, which could guide medical therapies based on the inflammatory profile observed. If future studies show certain inflammatory endotypes nearly always transition from early-stage to late-stage CRS, or from ARS to CRS, then medical therapies targeting these inflammatory pathways may prevent further disease progression. Endotyping may also help tailor medical therapies for individuals with frank CRS. For example, individuals diagnosed with CRS who have normal or low IgE levels have been shown to have greater symptomatic control under macrolide (a class of antibiotics) therapy.[34]

7.3 Final remarks

The studies described in this dissertation have contributed to the CRS literature in important and novel ways. We provided the first study to comparatively assess NSS exacerbation definitions relevant to CRS; the first study to quantify the workplace impacts of NSS from several related and overlapping conditions; and the first study to propose an approach to categorizing radiologic inflammation in sinus disease that takes into consideration location and patterns of opacification. Additional studies of CRS endotypes, resource utilization, and outcomes are necessary; however, our studies have shown that traditional approaches to defining CRS_S and CRS_O are likely incorrect. Therefore, it will be imperative to identify novel approaches to defining CRS_C before we can begin to understand its associated risks and impacts.

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Appendix

7.5 CRISP longitudinal study questionnaires

7.5.1 Baseline questionnaire

Study ID_____

Population Study of Nasal and Sinus Symptoms

Please answer each question to the best of your ability. Please complete this survey in one sitting. It should take around 10 to 15 minutes to complete. Use a pen to answer your questions. Please return the survey using the included self-addressed stamped envelope. Thank you for your time!

In your lifetime, have you ever had ...			
1.	Blockage of your nasal passages (nasal congestion) that lasted 3 months?	☐ Yes	☐ No
2.	Nasal discharge (runny nose) that was non-clear, green or yellow in color that lasted 3 months?	☐ Yes	☐ No
3.	Post-nasal drip (mucus dripping from the back of the nose into your throat) that lasted 3 months?	☐ Yes	☐ No
4.	Loss of sense of smell that lasted three months?	☐ Yes	☐ No
5.	Facial pain that lasted three months?	☐ Yes	☐ No
6.	Facial pressure that lasted three months?	☐ Yes	☐ No

SKIP NOTICE: If you answered "no" to all six questions above (questions #1-6), then skip to question #33.

7.	My nasal and sinus symptoms are only a problem during some seasons.	☐ Yes	☐ No	
8.	My nasal and sinus symptoms happen when I do NOT have a cold or flu.	☐ Yes	☐ No	
9.	At what age did you start experiencing the nasal or sinus symptoms listed in questions 1 through 6 for more than 3 months at a time?	☐ 0-10 ☐ 11-15 ☐ 16-20 ☐ 21-25	☐ 26-30 ☐ 31-35 ☐ 36-40 ☐ 41-45	☐ 46-50 ☐ 51-55 ☐ 56-60 ☐ Over 60

The questions below are about breathing and nasal problems you may have had in the past 3 months.

On average, how often in the past three months have you had ...		Never	Once in a while	Some of the time	Most of the time	All the time
10.	Blockage of your nasal passages (nasal congestion)?	☐	☐	☐	☐	☐
11.	Nasal discharge that was yellow or green in color?	☐	☐	☐	☐	☐
12.	Post-nasal drip?	☐	☐	☐	☐	☐
13.	Loss of sense of smell?	☐	☐	☐	☐	☐
14.	Facial pain?	☐	☐	☐	☐	☐
15.	Facial pressure?	☐	☐	☐	☐	☐

SKIP NOTICE: If you answered "never" or "once in a while" to all six questions #10-15, then skip to question #33.

Check the box that describes how often each problem below has happened in the past three months, on average.		Never	Once in a while	Some of the time	Most of the time	All the time
16.	Both of my nasal passages have blockage.	☐	☐	☐	☐	☐
17.	At least one of my nasal passages is completely blocked.	☐	☐	☐	☐	☐
18.	I have been very bothered by my blocked nasal passage(s).	☐	☐	☐	☐	☐
19.	I have a lot of nasal discharge.	☐	☐	☐	☐	☐
20.	I have to blow my nose more than 10 times a day because of my nasal discharge.	☐	☐	☐	☐	☐
21.	I have been very bothered by my nasal discharge.	☐	☐	☐	☐	☐
22.	I have been coughing after I eat or lie down	☐	☐	☐	☐	☐
23.	I have had mucus in my throat that felt like a lump or blockage.	☐	☐	☐	☐	☐
24.	I have been very bothered by my post-nasal drip.	☐	☐	☐	☐	☐

In the past 3 months, on average...		Never	Once in a while	Some of the time	Most of the time	All the time
25.	I have not been able to smell anything.	☐	☐	☐	☐	☐
26.	I have been very bothered by my loss of sense of smell.	☐	☐	☐	☐	☐
27.	On a scale of 0 to 10, my facial pain has been at least a 5. (0 is no pain and 10 is worst possible pain.)	☐	☐	☐	☐	☐
28.	I have been very bothered by my facial pain.	☐	☐	☐	☐	☐
29.	My facial pressure has been severe.	☐	☐	☐	☐	☐
30.	I have been very bothered by my facial pressure.	☐	☐	☐	☐	☐
31.	Where have you had facial pain in the past 3 months?	☐ Section 1 ☐ Section 2 ☐ Section 3 ☐ Section 4 ☐ I have not had facial pain				
32.	Where have you had facial pressure in the past 3 months?	☐ Section 1 ☐ Section 2 ☐ Section 3 ☐ Section 4 ☐ I have not had facial pain				

Check the box that describes how often, on average, you had the following problems in the past three months.

	SYMPTOM	Never	Once in a while	Some of the time	Most of the time	All the time
33.	Headaches	☐	☐	☐	☐	☐
34.	Fevers	☐	☐	☐	☐	☐
35.	Coughing	☐	☐	☐	☐	☐
36.	Bad breath	☐	☐	☐	☐	☐
37.	Fatigue	☐	☐	☐	☐	☐
38.	Nasal Itching	☐	☐	☐	☐	☐
39.	Sneezing	☐	☐	☐	☐	☐
40.	Eye Itching	☐	☐	☐	☐	☐
41.	Eye tearing	☐	☐	☐	☐	☐
42.	Ear fullness	☐	☐	☐	☐	☐
43.	Ear pain	☐	☐	☐	☐	☐
44.	Ear pressure	☐	☐	☐	☐	☐
45.	Wheezing (breathing with whistling sound in chest)	☐	☐	☐	☐	☐
46.	Chest tightness	☐	☐	☐	☐	☐
47.	Shortness of breath	☐	☐	☐	☐	☐
48.	Cold/ flu symptoms	☐	☐	☐	☐	☐

Check "YES" next to medications you have taken for sinus problems over the past three months. Include medications your doctor prescribed and over the counter medications. If you have not taken medication for sinus problems, check "NO."

49.	**Antibiotics** (Examples: Z-pack, Augmentin, Amoxicillin, Azithromycin, Doxycycline, Cipro, Levaquin)	☐ Yes	☐ No
50.	**Steroid pills** (Examples: Prednisone, Medrol dose pack, Methylprednisolone)	☐ Yes	☐ No
51.	**Nasal steroid sprays** (Examples: Nasonex, Mometasone, Flonase, Fluticasone)	☐ Yes	☐ No
52.	**Antihistamine pills** (Examples: Allegra, Claritin, Clarinase, Zyrtec)	☐ Yes	☐ No
53.	**Nasal antihistamines** (Examples: Astelin, Astepro, Azelastine, Patanase, Olopatidine)	☐ Yes	☐ No
54.	**Decongestants** (Examples: Sudafed, Afrin)	☐ Yes	☐ No

Please answer the questions below about sinus surgery.			
55.	How many times have you had sinus surgery?	☐ 0 – SKIP to question 57. ☐ 1	☐ 2 ☐ 3 or more
56.	Why did you have sinus surgery? (Check all that apply)	☐ Chronic rhinosinusitis ☐ Other: _____	☐ Nasal polyps ☐ Don't know
Check "yes" if a doctor has ever told you that you have any of these health problems.			
57.	Migraines	☐ Yes	☐ No
58.	Sinus problems	☐ Yes	☐ No
59.	Nasal polyps	☐ Yes	☐ No
60.	Asthma that is made worse by aspirin (aspirin intolerant asthma)	☐ Yes	☐ No
61.	Hay fever (seasonal allergies)	☐ Yes	☐ No
62.	Lupus	☐ Yes	☐ No
63.	Rheumatoid arthritis	☐ Yes	☐ No
64.	Psoriasis	☐ Yes	☐ No
65.	Inflammatory bowel disease	☐ Yes	☐ No
66.	Chronic rhinosinusitis (CRS) (If NO, SKIP to question #68)	☐ Yes	☐ No
67.	What test(s) did the doctor to do to test for CRS? (Check all that apply)	☐ CAT Scan ☐ Endoscopy ☐ MRI	☐ No test ☐ Don't know
Check "yes" if a doctor has ever told you that you have any of these health problems.			
68.	Nasal polyps (If NO, SKIP to question #70)	☐ Yes	☐ No
69.	What test(s) did the doctor to do to test for nasal polyps? (Check all that apply)	☐ CAT Scan ☐ Endoscopy ☐ MRI	☐ No test ☐ Don't know
70.	Have you ever had a blood test or skin test for allergies? (If NO, SKIP to question #72)	☐ Yes	☐ No
71.	Check the box next to the allergies that were found after a skin or blood test:	☐ Pollen ☐ Pets ☐ Mold ☐ Other: _____	☐ Don't know ☐ No allergies

Place a check in the box that describes any wheezing or whistling in the chest you have experienced.						
Check the box that describes how often each problem below has happened in the past twelve months.		Never	Once in a while	Some of the time	Most of the time	All the time
72.	Wheezing, chest tightness, or whistling in the chest when you did not have a cold or the flu.	☐	☐	☐	☐	☐
73.	Woken at night due to wheezing.	☐	☐	☐	☐	☐
74.	Chest has sounded wheezy during or after exercise.	☐	☐	☐	☐	☐
75.	Dry cough at night, apart from a cough from a cold or chest infection.	☐	☐	☐	☐	☐

Answer the following questions about asthma.			
76.	Have you ever been told by a doctor that you have asthma?	☐ Yes	☐ No – SKIP to question #80
77.	Have you had your asthma symptoms in the last 12 months?	☐ Yes	☐ No
78.	How old were you when your asthma first began?	___ ___ years old	
79.	How old were you when you had your most recent asthma symptoms?	___ ___ years old	

Answer the following questions about headaches you have had in the past 12 months.			
80.	How often do you have headaches?	☐ Never ☐ Once in a while ☐ Some of the time	☐ Most of the time ☐ All of the time
SKIP NOTICE: If you checked "never" or "once in a while", skip to question #84.			

Study ID_____

		Never	Rarely	Less than half the time	Half the time or more
81.	How often do your headaches interfere with your ability to work, study, or enjoy life?	☐	☐	☐	☐
82.	How often do you have nausea with your headaches?	☐	☐	☐	☐
83.	How often have you been unusually sensitive to light during your headaches?	☐	☐	☐	☐

Please respond to each question or statement by marking one box per row.

During the past 7 days...		Not at all	A little bit	Somewhat	Quite a bit	Very much
84.	I feel fatigued.	☐	☐	☐	☐	☐
85.	I have trouble starting things because I am tired.	☐	☐	☐	☐	☐
86.	How run-down did you feel on average?	☐	☐	☐	☐	☐
87.	How fatigued were you on average?	☐	☐	☐	☐	☐
88.	How much were you bothered by your fatigue on average?	☐	☐	☐	☐	☐
89.	To what degree did your fatigue interfere with your physical functioning?	☐	☐	☐	☐	☐
90.	How often did you have to push yourself to get things done because of your fatigue?	☐	☐	☐	☐	☐
91.	How often did you have trouble finishing things because of your fatigue?	☐	☐	☐	☐	☐

Please respond to the each question by marking one box per row.

92.	What is your current marital status?	☐ Married ☐ Separated ☐ Divorced	☐ Widowed ☐ Never Married ☐ Living with Partner	
93.	What is the highest grade of school or highest degree you have completed?	☐ No Schooling ☐ A few years ☐ Finished grammar school ☐ GED	☐ Some high school ☐ High school graduate ☐ Bachelor's degree	☐ Some college ☐ Associate degree ☐ Master's degree ☐ Doctoral degree
94.	About how much income did you receive last year before taxes and deductions?	☐ 0-9,999 ☐ 10,000-24,999 ☐ 25,000-49,999 ☐ 50,000-74,999	☐ 75,000-99,999 ☐ 100,000-149,999 ☐ 150,000+	

7.5.2 Six month follow-up (fall exacerbation) questionnaire

Study ID_____

Population Study of Nasal and Sinus Symptoms

Complete this survey in one sitting. It should take around 10 to 15 minutes. Use a pen. Answer each question as best you can. Please return the survey in the self-addressed stamped envelope. Thank you for your participation and help!

On average, how often in the past six months have you had...		Never	Once in a while	Some of the time	Most of the time	All the time
1	Blockage of your nasal passages (nasal congestion)?	☐	☐	☐	☐	☐
2	Nasal discharge that was yellow or green in color?	☐	☐	☐	☐	☐
3	Post-nasal drip?	☐	☐	☐	☐	☐
4	Loss of sense of smell?	☐	☐	☐	☐	☐
5	Facial pain?	☐	☐	☐	☐	☐
6	Facial pressure?	☐	☐	☐	☐	☐

If you answered "Never" or "Once in a while" to all questions above, skip to question 30.

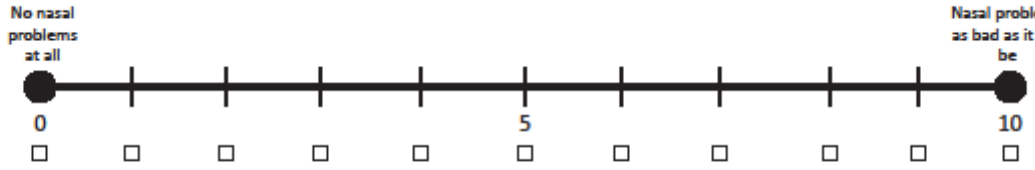
Check the box that describes how often each problem has happened in the past six months, on average		Never	Once in a while	Some of the time	Most of the time	All the time
7	Both of my nasal passages have blockage.	☐	☐	☐	☐	☐
8	At least one of my nasal passages is completely blocked.	☐	☐	☐	☐	☐
9	I have been very bothered by my nasal passage(s).	☐	☐	☐	☐	☐
10	I have a lot of nasal discharge.	☐	☐	☐	☐	☐
11	I have to blow my nose more than 10 times a day because of my nasal discharge.	☐	☐	☐	☐	☐
12	I have been very bothered by my nasal discharge.	☐	☐	☐	☐	☐
13	I have been coughing after I eat or lie down.	☐	☐	☐	☐	☐
14	I have had mucus in my throat that felt like a lump or blockage.	☐	☐	☐	☐	☐
15	I have been very bothered by my post-nasal drip.	☐	☐	☐	☐	☐
16	I have not been able to smell anything.	☐	☐	☐	☐	☐
17	I have been very bothered by my loss of sense of smell.	☐	☐	☐	☐	☐
18	On a scale of 0 to 10, my facial pain has been at least a 5. (0 is no pain and 10 is worst possible pain.)	☐	☐	☐	☐	☐
19	I have been very bothered by my facial pain.	☐	☐	☐	☐	☐
20	Where have you had facial pain?	☐ Section 1 ☐ Section 2 ☐ Section 3 ☐ Section 4 ☐ I have not had facial pain 				
21	My facial pressure has been severe.	☐	☐	☐	☐	☐
22	I have been very bothered by my facial pressure.	☐	☐	☐	☐	☐
23	Where have you had facial pressure?	☐ Section 1 ☐ Section 2 ☐ Section 3 ☐ Section 4 ☐ I have not had facial pressure 				

Study ID_____

Please check the answer that best describes how long you had each nasal problem in the past six months.				
		Lasted less than a month	Lasted more than a month, but less than 3 months	Lasted 3 months or more
24	Nasal blockage	☐	☐	☐
25	Nasal discharge	☐	☐	☐
26	Post-nasal drip	☐	☐	☐
27	Loss of smell	☐	☐	☐
28	Facial pain	☐	☐	☐
29	Facial pressure	☐	☐	☐

Please answer the following questions about sinus surgery.		
30	Have you had sinus surgery in the past six months?	☐ Yes ☐ No (If no skip to question 32)
31	Why did you have sinus surgery? (Check all that apply)	☐ Chronic Rhinosinusitis ☐ Nasal Polyps ☐ Other _____ ☐ Don't know

	How often in the past six months did you have the following symptoms?	Never	Once in a while	Some of the time	Most of the time	All of the time
32	Headaches	☐	☐	☐	☐	☐
33	Fevers	☐	☐	☐	☐	☐
34	Coughing	☐	☐	☐	☐	☐
35	Bad breath	☐	☐	☐	☐	☐
36	Fatigue	☐	☐	☐	☐	☐
37	Nasal itching	☐	☐	☐	☐	☐
38	Sneezing	☐	☐	☐	☐	☐
39	Eye itching	☐	☐	☐	☐	☐
40	Eye tearing	☐	☐	☐	☐	☐
41	Ear fullness	☐	☐	☐	☐	☐
42	Ear pain	☐	☐	☐	☐	☐
43	Ear pressure	☐	☐	☐	☐	☐
44	Wheezing (breathing with a whistling sound in chest)	☐	☐	☐	☐	☐
45	Chest tightness	☐	☐	☐	☐	☐
46	Shortness of breath	☐	☐	☐	☐	☐
47	Cold/flu symptoms	☐	☐	☐	☐	☐

The next questions are about how your symptoms have been over the past four weeks.		
48	Mark an X in the box below the number that indicate how severe your nasal and sinus symptoms have been over the last four weeks.	
49	My nasal problems in the past four weeks have been...	☐ Much better than usual (Skip to Question 63) ☐ Better than usual (Skip to Question 63) ☐ About the same (Skip to Question 63) ☐ Worse than usual (Continue) ☐ Much worse than usual (Continue)

Study ID_____

If your nasal problems are better than usual or about the same, skip to the end of the survey.		
50	In the past four weeks, my nasal problems...	☐ Got worse over two to four weeks ☐ Got worse over one to two weeks ☐ Got worse in a week or less
51	How long have your nasal problems in the past four weeks been worse than usual?	☐ Less than a week ☐ 1 to 2 weeks ☐ More than 2 weeks

Check the answer that describes how each nasal problem has changed over the past 4 weeks.						
		Much better than usual	Better than usual	About the same	Worse than usual	Much worse than usual
52	Blockage of your nasal passages (nasal congestion)	☐	☐	☐	☐	☐
53	Nasal discharge that was yellow or green in color	☐	☐	☐	☐	☐
54	Post-nasal drip	☐	☐	☐	☐	☐
55	Loss of sense of smell	☐	☐	☐	☐	☐
56	Facial pain	☐	☐	☐	☐	☐
57	Facial pressure	☐	☐	☐	☐	☐

Please indicate if you have taken any of the following actions for your worse than usual nasal and sinus symptoms in the past 4 weeks.			
58	Saw or called your doctor?	☐ Yes	☐ No
59	Used steroid pills?	☐ Yes	☐ No
60	Used antibiotics?	☐ Yes	☐ No
61	Used nasal steroid spray?	☐ Yes	☐ No
62	Used over the counter cold/allergy pills?	☐ Yes	☐ No

The following questions are about symptoms that may be connected to a number of health conditions. We want to understand how they might be related to nasal or sinus problems. Please rate how much you agree with each statement by checking one of the five answers for each question.						
		Very little	A little	Some	Much	Very Much
63	It is important not to appear nervous	☐	☐	☐	☐	☐
64	When I cannot keep my mind on task, I worry that I might be going crazy	☐	☐	☐	☐	☐
65	It scares me when I feel shaky	☐	☐	☐	☐	☐
66	It scares me when I feel faint	☐	☐	☐	☐	☐
67	It is important to me to stay in control of my emotions	☐	☐	☐	☐	☐
68	It scares me when I feel my heart beat rapidly	☐	☐	☐	☐	☐
69	It embarrasses me when my stomach growls	☐	☐	☐	☐	☐
70	It scares me when I am nauseous (sick stomach)	☐	☐	☐	☐	☐
71	When I notice my heart beating rapidly, I worry that I might be having a heart attack	☐	☐	☐	☐	☐
72	It scares me when I become short of breath	☐	☐	☐	☐	☐
73	When my stomach is upset, I worry that I might be seriously ill	☐	☐	☐	☐	☐
74	It scares me when I am unable to keep my mind on a task	☐	☐	☐	☐	☐
75	Other people notice when I feel shaky	☐	☐	☐	☐	☐
76	Unusual body sensations scare me	☐	☐	☐	☐	☐
77	When I am nervous, I worry that I might be mentally ill	☐	☐	☐	☐	☐
78	It scares me when I am nervous	☐	☐	☐	☐	☐

Study ID_____

Over the last 2 weeks, how often have you been bothered by any of the following problems? Please check the box for your answer.					
		Not at all	Several days	More than half the days	Nearly every day
79	Little interest or pleasure in doing things	☐	☐	☐	☐
80	Feeling down, depressed, or hopeless	☐	☐	☐	☐
81	Trouble falling asleep or staying asleep, or sleeping too much	☐	☐	☐	☐
82	Feeling tired or having little energy	☐	☐	☐	☐
83	Poor appetite or overeating	☐	☐	☐	☐
84	Feeling bad about yourself---or that you are a failure or have let yourself or your family down	☐	☐	☐	☐
85	Trouble concentrating on things, such as reading the newspaper or watching television	☐	☐	☐	☐
86	Moving or speaking so slowly that other people could have noticed? Or the opposite---being so fidgety or restless that you have been moving around a lot more than usual	☐	☐	☐	☐
		Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
87	If you checked any of the problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?	☐	☐	☐	☐

7.5.3 Winter exacerbation questionnaire

Study ID_____

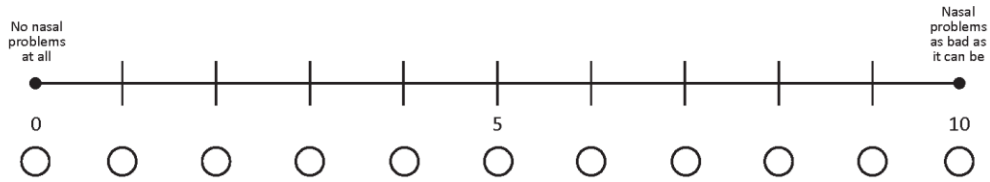
Thank you for your continued contributions to the chronic rhinosinusitis study of your nasal and sinus symptoms. We are contacting you now because we want to understand how symptoms might change with the seasons. We hope you will continue to complete these surveys. **This one is much shorter, less than one page.** Thank you for your time!

Population Study of Nasal and Sinus Symptoms-Exacerbations

Complete this survey in one sitting. It should take around 5 minutes. Use a pen, fill in the circle completely. Answer each question as best you can. Please return the survey in the self-addressed stamped envelope. Thank you for your participation and help!

The next questions are about how your symptoms have been over the past four weeks.

1. Mark an X in the circle below the number that indicates how severe your nasal and sinus symptoms have been over the last four weeks.



2. My nasal problems in the past 4 weeks have been...
   - ○ Much better than usual (You are done. Thank you!)
   - ○ Better than usual (You are done. Thank you!)
   - ○ About the same (You are done. Thank you!)
   - ○ Worse than usual (Continue)
   - ○ Much worse than usual (Continue)

If your nasal problems are better than usual or about the same, you are done. No need to continue.

3. In the past four weeks, my nasal problems...
   - ○ Got worse over two to four weeks
   - ○ Got worse over one to two weeks
   - ○ Got worse in a week or less

4. How long have your nasal problems in the past four weeks been worse than usual?
   - ○ Less than a week
   - ○ 1 to 2 weeks
   - ○ More than 2 weeks

Check the answer that describes how each nasal problem has changed over the past 4 weeks.

		Much better than usual	Better than usual	About the same	Worse than usual	Much worse than usual
5	Blockage of your nasal passages (nasal congestion)	○	○	○	○	○
6	Nasal discharge that was yellow or green in color	○	○	○	○	○
7	Post-nasal drip	○	○	○	○	○
8	Loss of sense of smell	○	○	○	○	○
9	Facial pain	○	○	○	○	○
10	Facial pressure	○	○	○	○	○

Please indicate if you have taken any of the following actions for your worse than usual nasal and sinus symptoms in the past four weeks.

11	Saw or called your doctor?	○ Yes	○ No
12	Used steroid pills?	○ Yes	○ No
13	Used antibiotics?	○ Yes	○ No
14	Used nasal steroid spray?	○ Yes	○ No
15	Used over the counter cold/allergy pills?	○ Yes	○ No

7.5.4 Spring exacerbation questionnaire

Study ID_____

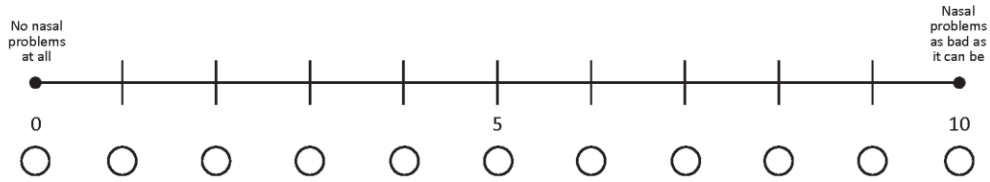
Thank you for your continued contributions to the chronic rhinosinusitis study of your nasal and sinus symptoms. We are contacting you again because we want to continue to understand how symptoms might change with the seasons. You may have recently completed this survey; this current survey is for the **spring season**. We hope you will continue to complete these surveys. **This is short, only one page**. Thank you for your time!

Population Study of Nasal and Sinus Symptoms-Exacerbations

Complete this survey in one sitting. It should take around 5 minutes. Use a pen, fill in the circle completely. Answer each question as best you can. Please return the survey in the self-addressed stamped envelope. Thank you for your participation and help!

The next questions are about how your symptoms have been over the past four weeks.

1. Mark an X in the circle below the number that indicates how severe your nasal and sinus symptoms have been over the last four weeks.



2. My nasal problems in the past 4 weeks have been...
   - ○ Much better than usual (You are done. Thank you!)
   - ○ Better than usual (You are done. Thank you!)
   - ○ About the same (You are done. Thank you!)
   - ○ Worse than usual (Continue)
   - ○ Much worse than usual (Continue)

If your nasal problems are better than usual or about the same, you are done. No need to continue.

3. In the past four weeks, my nasal problems...
   - ○ Got worse over two to four weeks
   - ○ Got worse over one to two weeks
   - ○ Got worse in a week or less

4. How long have your nasal problems in the past four weeks been worse than usual?
   - ○ Less than a week
   - ○ 1 to 2 weeks
   - ○ More than 2 weeks

Check the answer that describes how each nasal problem has changed over the past 4 weeks.

		Much better than usual	Better than usual	About the same	Worse than usual	Much worse than usual
5	Blockage of your nasal passages (nasal congestion)	○	○	○	○	○
6	Nasal discharge that was yellow or green in color	○	○	○	○	○
7	Post-nasal drip	○	○	○	○	○
8	Loss of sense of smell	○	○	○	○	○
9	Facial pain	○	○	○	○	○
10	Facial pressure	○	○	○	○	○

Please indicate if you have taken any of the following actions for your worse than usual nasal and sinus symptoms in the past four weeks.

11	Saw or called your doctor?	○ Yes	○ No
12	Used steroid pills?	○ Yes	○ No
13	Used antibiotics?	○ Yes	○ No
14	Used nasal steroid spray?	○ Yes	○ No
15	Used over the counter cold/allergy pills?	○ Yes	○ No

7.5.5 16-month follow-up (summer exacerbation) questionnaire

Study ID: _____

Population Study of Nasal and Sinus Symptoms

Complete this survey in one sitting. It should take around 10 to 15 minutes. Fill in the circle completely. Use a pen. Answer each question as best you can. Please return the survey in the self-addressed stamped envelope. Thank you for your participation and help!

On average, how often in the past three months have you had...		Never	Once in a while	Some of the time	Most of the time	All the time
1	Blockage of your nasal passages (nasal congestion)?	○	○	○	○	○
2	Nasal discharge that was yellow or green in color?	○	○	○	○	○
3	Post-nasal drip?	○	○	○	○	○
4	Loss of sense of smell?	○	○	○	○	○
5	Facial pain?	○	○	○	○	○
6	Facial pressure?	○	○	○	○	○
Fill in the circle that describes how often each problem has happened in the past three months, on average		**Never**	**Once in a while**	**Some of the time**	**Most of the time**	**All the time**
7	Both of my nasal passages have blockage.	○	○	○	○	○
8	At least one of my nasal passages is completely blocked.	○	○	○	○	○
9	I have been very bothered by my blocked nasal passage(s).	○	○	○	○	○
10	I have a lot of nasal discharge.	○	○	○	○	○
11	I have to blow my nose more than 10 times a day because of my nasal discharge.	○	○	○	○	○
12	I have been very bothered by my nasal discharge.	○	○	○	○	○
13	I have been coughing after I eat or lie down.	○	○	○	○	○
14	I have had mucus in my throat that felt like a lump or blockage.	○	○	○	○	○
15	I have been very bothered by my post-nasal drip.	○	○	○	○	○
16	I have not been able to smell anything.	○	○	○	○	○
17	I have been very bothered by my loss of sense of smell.	○	○	○	○	○
18	On a scale of 0 to 10, my facial pain has been at least a 5. (0 is no pain and 10 is worst possible pain.)	○	○	○	○	○
19	I have been very bothered by my facial pain.	○	○	○	○	○
20	Where have you had facial pain in the past 3 months?	○ Section 1 ○ Section 2 ○ Section 3 ○ Section 4 ○ I have not had facial pain				
Fill in the circle that describes how often each problem has happened in the past three months, on average		**Never**	**Once in a while**	**Some of the time**	**Most of the time**	**All the time**
21	My facial pressure has been severe.	○	○	○	○	○
22	I have been very bothered by my facial pressure.	○	○	○	○	○
23	Where have you had facial pressure in the past 3 months?	○ Section 1 ○ Section 2 ○ Section 3 ○ Section 4 ○ I have not had facial pain				
Please answer the following questions about sinus surgery						
24	Have you had sinus surgery in the past six months?	○ Yes ○ No				
25	Why did you have sinus surgery? (Check all that apply)	○ Chronic Rhinosinusitis ○ Nasal polyps ○ Other _____ ○ Don't know				

How often in the past three months did you have the following symptoms?		Never	Once in a while	Some of the time	Most of the time	All the time
26	Headaches	○	○	○	○	○
27	Fevers	○	○	○	○	○
28	Coughing	○	○	○	○	○
29	Bad breath	○	○	○	○	○
30	Fatigue	○	○	○	○	○
31	Nasal itching	○	○	○	○	○
32	Sneezing	○	○	○	○	○
33	Eye itching	○	○	○	○	○
34	Eye tearing	○	○	○	○	○
35	Ear fullness	○	○	○	○	○
36	Ear pain	○	○	○	○	○
37	Ear pressure	○	○	○	○	○
38	Wheezing (breathing with a whistling sound in chest)	○	○	○	○	○
39	Chest tightness	○	○	○	○	○
40	Shortness of breath	○	○	○	○	○
41	Cold/ flu symptoms	○	○	○	○	○

The next questions are about how your symptoms have been over the past four weeks.

42	Fill in the circle completely below the number that indicates how severe your nasal and sinus symptoms have been over the last four weeks. No nasal problems at all — Nasal problems as bad as it can be 0 ○ ○ ○ ○ ○ 5 ○ ○ ○ ○ 10 ○	
43	My nasal problems in the past four weeks have been...	○ Much better than usual (Skip to Question 57) ○ Better than usual (Skip to Question 57) ○ About the same (Skip to Question 57) ○ Worse than usual (Continue) ○ Much worse than usual (Continue)

If your nasal problems are better than usual or about the same, skip to Question 57.

44	In the past four weeks, my nasal problems...	○ Got worse over two to four weeks ○ Got worse over one to two weeks ○ Got worse in a week or less
45	How long have your nasal problems in the past four weeks been worse than usual?	○ Less than a week ○ One to two weeks ○ More than two weeks

Fill in the circle that describes how each nasal problem has changed over the past four weeks.		Much better than usual	Better than usual	About the same	Worse than usual	Much worse than usual
46	Blockage of your nasal passages (nasal congestion)	○	○	○	○	○
47	Nasal discharge that was yellow or green in color	○	○	○	○	○
48	Post-nasal drip	○	○	○	○	○
49	Loss of sense of smell	○	○	○	○	○
50	Facial pain	○	○	○	○	○
51	Facial pressure	○	○	○	○	○

Please indicate if you have taken any of the following actions for your worse than usual nasal and sinus symptoms in the past 4 weeks.			
52	Saw or called your doctor?	○ Yes	○ No
53	Used steroid pills?	○ Yes	○ No
54	Used antibiotics?	○ Yes	○ No
55	Used nasal steroid spray?	○ Yes	○ No
56	Used over the counter cold/ allergy pills?	○ Yes	○ No
The next questions ask about being exposed to dust or fumes in your work.			
In any current or past job that you have held, have you ever been exposed to:			
57	Dust from rock, sand, concrete, coal, asbestos, silica or soil?	○ Yes	○ No
58	Dust from baking flours, grains, wood, cotton, plants or animals?	○ Yes	○ No
59	Exhaust fumes from trucks, buses, heavy machinery or diesel engines?	○ Yes	○ No
Please answer the following questions about smoking.			
60	Does anyone who lives in your home smoke cigarettes, cigars, or pipes anywhere inside the home?	○ Yes	○ No (If no, skip to question 63)
61	What are the total number of smokers in the home (don't count yourself)	○ 1-2	○ 3 or more
62	During the past seven days, on how many days did someone smoke inside the home?	_____ DAYS in the past 7 days	
Please answer the following questions about your job. (If you are not currently working, skip to question 75)			
63	How many DAYS do you usually work each week?	_____ DAYS per week	
64	How many HOURS do you usually work each day?	_____ HOURS per day	
The next questions are about time you may have missed from work in the PAST 2 WEEKS.			
65	How many workdays did you miss in the PAST TWO WEEKS because you were not feeling well?	_____ (If none, skip to question 67)	
66	How many of the workdays in the PAST TWO WEEKS were missed due to nasal and sinus symptoms	_____	
67	On how many days in the PAST TWO WEEKS did you go to work when you were not feeling well?	_____DAYS in the past 2 weeks (If none, skip to question 75)	
68	On the days in the PAST TWO WEEKS you were not feeling well at work how many were due to your nasal and sinus symptoms?	_____DAYS	
69	When you weren't feeling well due to your nasal and sinus symptoms, how long, on average, did it take you to start working after you got to work?	_____MINUTES OR _____HOURS OR	

Study ID: _____

The next questions are about the day or days that you went to work not feeling well related to your nasal and sinus symptoms.		All of the time	Most of the time	About half the time	Some of the time	None of the time
70	On the day(s) you went to work with nasal and sinus symptoms, on average, how much of the time did you just do no work when you were supposed to be working?	○	○	○	○	○
71	On the day(s) you went to work with nasal and sinus symptoms, how much of the time did you spend doing a job over because you made a mistake or your supervisor told you to do a job over?	○	○	○	○	○
72	On the day(s) you went to work with nasal and sinus symptoms, how much of the time did you find it difficult to concentrate on what you needed to do?	○	○	○	○	○
73	On the day(s) you went to work with nasal and sinus symptoms, how much of the time did you work more slowly or take longer to complete tasks than usual or expected?	○	○	○	○	○
74	On the day(s) you went to work with nasal and sinus symptoms, how much of the time were you very tired, fell asleep at work or just felt too exhausted to do your work?	○	○	○	○	○

These next questions are about where you live			
75	Do you have contact with an animal in or around your home?	Dog	○ Yes ○ No ○ Don't know
		Cat	○ Yes ○ No ○ Don't know
		Farm animal	○ Yes ○ No ○ Don't know
76	Do you live on a farm?	○ Yes ○ No (If no, skip to question 78)	
77	What type of farm? (Check all that apply)	○ Livestock ○ Crops ○ Other	
78	Do you work on a farm?	○ Yes ○ No (If no, you are done)	
79	What type of farm? (Check all that apply)	○ Livestock ○ Crops ○ Other	

7.6 CRISP CT study questionnaire

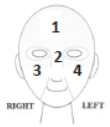
7.6.1 CT study questionnaire, version 1

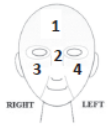
Population Study of Nasal and Sinus Symptoms-CT Scan

Please complete this survey in one sitting. We would like to know how your symptoms are currently. It should take around 5 minutes. Use a pen. Answer each question as best you can. Thank you for your participation and help!

On average, how often in the past three months have you had...		Never	Once in a while	Some of the time	Most of the time	All the time
1.	Blockage of your nasal passages (nasal congestion)?	☐	☐	☐	☐	☐
2.	Nasal discharge that was yellow or green in color?	☐	☐	☐	☐	☐
3.	Post-nasal drip?	☐	☐	☐	☐	☐
4.	Loss of sense of smell?	☐	☐	☐	☐	☐
5.	Facial pain?	☐	☐	☐	☐	☐
6.	Facial pressure?	☐	☐	☐	☐	☐

Check the box that describes how often each problem below has happened in the past three months, on average.		Never	Once in a while	Some of the time	Most of the time	All the time
7.	Both of my nasal passages have blockage.	☐	☐	☐	☐	☐
8.	At least one of my nasal passages is completely blocked.	☐	☐	☐	☐	☐
9.	I have been very bothered by my blocked nasal passage(s).	☐	☐	☐	☐	☐
10.	I have a lot of nasal discharge.	☐	☐	☐	☐	☐
11.	I have to blow my nose more than 10 times a day because of my nasal discharge.	☐	☐	☐	☐	☐
12.	I have been very bothered by my nasal discharge.	☐	☐	☐	☐	☐
13.	I have been coughing after I eat or lie down.	☐	☐	☐	☐	☐
14.	I have had mucus in my throat that felt like a lump or blockage.	☐	☐	☐	☐	☐
15.	I have been very bothered by my post-nasal drip.	☐	☐	☐	☐	☐
16.	I have not been able to smell anything.	☐	☐	☐	☐	☐
17.	I have been very bothered by my loss of sense of smell.	☐	☐	☐	☐	☐
18.	On a scale of 0 to 10, my facial pain has been at least a 5. (0 is no pain and 10 is worst possible pain.)	☐	☐	☐	☐	☐
19.	I have been very bothered by my facial pain.	☐	☐	☐	☐	☐
20.	My facial pressure has been severe.	☐	☐	☐	☐	☐
21.	I have been very bothered by my facial pressure.	☐	☐	☐	☐	☐
22.	Where have you had facial pain in the past 3 months?	☐ Section 1 ☐ Section 2 ☐ Section 3 ☐ Section 4 ☐ I have not had facial pain				
23.	Where have you had facial pressure in the past 3 months?	☐ Section 1 ☐ Section 2 ☐ Section 3 ☐ Section 4 ☐ I have not had facial pain				





Please continue to the back page to answer additional questions

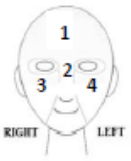
Check the box that describes how often, on average, you had the following problems in the past three months.						
SYMPTOM		Never	Once in a while	Some of the time	Most of the time	All the time
24.	Headaches	☐	☐	☐	☐	☐
25.	Fevers	☐	☐	☐	☐	☐
26.	Coughing	☐	☐	☐	☐	☐
27.	Bad breath	☐	☐	☐	☐	☐
28.	Fatigue	☐	☐	☐	☐	☐
29.	Nasal itching	☐	☐	☐	☐	☐
30.	Sneezing	☐	☐	☐	☐	☐
31.	Eye itching	☐	☐	☐	☐	☐
32.	Eye tearing	☐	☐	☐	☐	☐
33.	Ear fullness	☐	☐	☐	☐	☐
34.	Ear pain	☐	☐	☐	☐	☐
35.	Ear pressure	☐	☐	☐	☐	☐
36.	Wheezing (breathing with whistling sound in chest)	☐	☐	☐	☐	☐
37.	Chest tightness	☐	☐	☐	☐	☐
38.	Shortness of breath	☐	☐	☐	☐	☐
39.	Cold/flu symptoms	☐	☐	☐	☐	☐
Please answer the following questions about sinus surgery.						
40.	Have you had sinus surgery for chronic rhinosinusitis in the past year?			☐ Yes	☐ No	
41.	Have you had nasal polyp surgery in the past year?			☐ Yes	☐ No	

7.6.2 CT study questionnaire, version 2

Study ID_«Study_ID_Number»__

Population Study of Nasal and Sinus Symptoms

Please complete this survey in one sitting. We would like to know how your symptoms have been over the past 3 months. It should take around 5 minutes. Use a pen. Answer each question as best you can. Thank you for your participation and help!

On average, how often in the past three months have you had …		Never	Once in a while	Some of the time	Most of the time	All the time
1.	Blockage of your nasal passages (nasal congestion)?	☐	☐	☐	☐	☐
2.	Nasal discharge that was yellow or green in color?	☐	☐	☐	☐	☐
3.	Post-nasal drip?	☐	☐	☐	☐	☐
4.	Loss of sense of smell?	☐	☐	☐	☐	☐
5.	Facial pain?	☐	☐	☐	☐	☐
6.	Facial pressure?	☐	☐	☐	☐	☐
Check the box that describes how often, on average, you had the following problems in the past 3 months.		**Never**	**Once in a while**	**Some of the time**	**Most of the time**	**All the time**
7.	Both of my nasal passages have blockage.	☐	☐	☐	☐	☐
8.	At least one of my nasal passages is completely blocked.	☐	☐	☐	☐	☐
9.	I have been very bothered by my blocked nasal passage(s).	☐	☐	☐	☐	☐
10.	I have a lot of nasal discharge.	☐	☐	☐	☐	☐
11.	I have to blow my nose more than 10 times a day because of my nasal discharge.	☐	☐	☐	☐	☐
12.	I have been very bothered by my nasal discharge.	☐	☐	☐	☐	☐
13.	I have been coughing after I eat or lie down	☐	☐	☐	☐	☐
14.	I have had mucus in my throat that felt like a lump or blockage.	☐	☐	☐	☐	☐
15.	I have been very bothered by my post-nasal drip.	☐	☐	☐	☐	☐
16.	I have not been able to smell anything.	☐	☐	☐	☐	☐
17.	I have been very bothered by my loss of sense of smell.	☐	☐	☐	☐	☐
18.	On a scale of 0 to 10, my facial pain has been at least a 5. (0 is no pain and 10 is worst possible pain.)	☐	☐	☐	☐	☐
19.	I have been very bothered by my facial pain.	☐	☐	☐	☐	☐
20.	My facial pressure has been severe.	☐	☐	☐	☐	☐
21.	I have been very bothered by my facial pressure.	☐	☐	☐	☐	☐
22.	Where have you had facial pain in the past 3 months?	☐ Section 1 ☐ Section 2 ☐ Section 3 ☐ Section 4 ☐ I have not had facial pain				
23.	My nasal and sinus symptoms are only a problem during some seasons	☐ Yes	☐ No			
24.	My nasal and sinus symptoms happen when I do NOT have a cold or flu.	☐ Yes	☐ No			

Check the box that describes how often, on average, you had the following symptoms in the past 3 months.		Never	Once in a while	Some of the time	Most of the time	All of the time
26.	Fevers	☐	☐	☐	☐	☐
25.	Coughing	☐	☐	☐	☐	☐
26.	Bad breath	☐	☐	☐	☐	☐
27.	Nasal itching	☐	☐	☐	☐	☐
28.	Sneezing	☐	☐	☐	☐	☐
29.	Eye itching	☐	☐	☐	☐	☐
30.	Eye tearing	☐	☐	☐	☐	☐
31.	Ear fullness	☐	☐	☐	☐	☐
32.	Ear pain	☐	☐	☐	☐	☐
33.	Ear pressure	☐	☐	☐	☐	☐
34.	Shortness of breath	☐	☐	☐	☐	☐
35.	Cold/flu symptoms	☐	☐	☐	☐	☐
Place a check in the box that describes any wheezing or whistling in the chest you have experienced.						
Check the box that describes how often each problem below has happened in the past 3 months.		Never	Once in a while	Some of the time	Most of the time	All the time
36.	Wheezing, chest tightness, or whistling in the chest when you did not have a cold or the flu	☐	☐	☐	☐	☐
37.	Woken at night due to wheezing	☐	☐	☐	☐	☐
38.	Chest has sounded wheezy during or after exercise	☐	☐	☐	☐	☐
39.	Dry cough at night, apart from a cough from a cold or chest infection	☐	☐	☐	☐	☐

Answer the following questions about headaches you have had in the past 3 months.		Never	Rarely	Less than half the time	Half the time or more
40.	How often do your headaches interfere with your ability to work, study, or enjoy life?	☐	☐	☐	☐
41.	How often do you have nausea with your headaches?	☐	☐	☐	☐
42.	How often have you been unusually sensitive to light during your headaches?	☐	☐	☐	☐

Please respond to each question or statement by marking one box per row.						
During the past 7 days...		Not at all	A little bit	Somewhat	Quite a bit	Very much
43.	I feel fatigued.	☐	☐	☐	☐	☐
44.	I have trouble starting things because I am tired.	☐	☐	☐	☐	☐
45.	How run-down did you feel on average?	☐	☐	☐	☐	☐
46.	How fatigued were you on average?	☐	☐	☐	☐	☐
47.	How much were you bothered by your fatigue on average?	☐	☐	☐	☐	☐
48.	To what degree did your fatigue interfere with your physical functioning?	☐	☐	☐	☐	☐
49.	How often did you have to push yourself to get things done because of your fatigue?	☐	☐	☐	☐	☐
50.	How often did you have trouble finishing things because of your fatigue?	☐	☐	☐	☐	☐

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Nasal and sinus symptoms and chronic rhinosinusitis in a population-based sample

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Abstract

Background: The objective of this study was to describe the first US-based study to use the European Position Paper on Rhinosinusitis (EPOS) criteria to study the prevalence of chronic rhinosinusitis (CRS) in a general-population sample.
Methods: A CRS symptom questionnaire was mailed to 23 700 primary care patients from Geisinger Clinic, a health system serving 45 counties in Pennsylvania. CRS cases were categorized into four unique subgroups based on EPOS symptoms: obstruction and discharge with no smell loss or pain/pressure; smell loss without pain/pressure; facial pain and/or pressure without smell loss; and both smell loss and pain/pressure. All cases were required to have nasal obstruction or discharge. Logistic regression was used to evaluate potential factors associated with CRS subgroups.
Results: We found that 11.9% of patients met criteria for CRS. Prevalence peaked at 15.9% between ages 50 and 59 years and then dropped to 6.8% after age 69. The odds of CRS was higher among patients who were white, younger, smokers, had a history of Medical Assistance, and had other diseases. When CRS subgroups were modeled separately, these associations were no longer significant for some CRS subgroups. Comorbid diseases were most strongly associated with CRS cases who reported smell loss and facial pain and/or pressure and had the weakest associations with CRS cases who did not report these symptoms.
Conclusions: CRS is a highly prevalent and heterogeneous condition. Differences in risk factors and health outcomes across symptom subgroups may be indicative of differences in etiology that have implications for disease management.

Chronic rhinosinusitis (CRS) is defined by the presence of nasal and sinus symptoms for at least 3 months accompanied by objective evidence of sinus inflammation documented by either sinus computed tomography (CT) scan or endoscopy. The requirement for objective evidence has been an obstacle to large-scale, population-based studies of CRS. Knowledge of CRS is primarily derived from smaller studies of patients in tertiary healthcare settings (1). We describe the first large-scale epidemiologic profile of CRS based in the United States using consensus criteria developed for epidemiologic studies.

The European Position Paper on Rhinosinusitis (EPOS) created criteria for CRS to be used in epidemiologic studies but without the need for objective evidence. EPOS criteria require nasal and sinus symptoms lasting at least 12 weeks with or without objective evidence of disease (2). This symptom-based definition has been used to study the prevalence of CRS in Europe (10.9%), China (8%), and Brazil (5.5%), with a twofold range of estimates (3–5). The differences in prevalence estimates have been attributed to geographic and demographic variation across studies (3). To date, there is no

estimate for the prevalence of CRS using EPOS criteria in any US population-based sample. The most widely cited study in the US population, based on data from the National Health Interview Study, relied on self-reported doctor's diagnosis of sinusitis, not CRS, and did not distinguish acute from chronic sinusitis (6).

The Chronic Rhinosinusitis Integrative Studies Program (CRISP) conducted the first US-based study to use the EPOS criteria to study the prevalence of chronic rhinosinusitis (CRS) using a general-population sample from Pennsylvania (2). The goals of this study were to describe the epidemiology of CRS in the general population and to identify associated sociodemographic factors, health behaviors, and comorbidities.

Methods

Study overview

A self-administered questionnaire was mailed to a stratified random sample of 23 700 primary care patients from Geisinger Clinic (GC) to obtain data on sociodemographics, sinus symptoms, other relevant symptoms (e.g., headache, fatigue), diagnoses, and diagnostic procedures and treatments for sinus disease. We estimated age- and sex-specific prevalence of EPOS-defined CRS epidemiologic criteria based on symptoms only, hereafter referred to as CRS, and characterized CRS symptom subgroups. The study was approved by Geisinger Health System's Institutional Review Board.

Study population and subject selection

GC serves more than 400 000 primary care patients across a 45-county area in Pennsylvania. The primary care population is representative of the general population in the region (7). GC EHR data from 2006 to 2013 were used to categorize all adult primary care patients into one of three groups based on history of sinus-related diagnoses and/or evaluations in the EHR. The 'CRS Code' group (n = 13 494) had at least two ICD-9 codes for CRS (International Classification of Diseases [ICD]-9 codes 473.x or 471.x) associated with an outpatient, inpatient, or emergency department encounter or had at least one Current Procedural Terminology (CPT) code for sinus computerized tomography (CT), sinus endoscopy, or sinus surgery. The 'Asthma/Allergy Code' group (n = 49 918) had at least one ICD-9 code for asthma (493.x) or allergic rhinitis (477.x), or a single ICD-9 code for CRS associated with an outpatient, inpatient, or emergency department encounter. The 'No Sinus Codes' group consisted of 200 769 patients with no history of asthma, allergic rhinitis, CRS, or sinus-related CPT codes in the record.

A random sample of 23 700 primary care patients, stratified by race (white/nonwhite) and EHR history (CRS Code, Asthma/Allergy Code, No Sinus Codes), was sent the questionnaire. To ensure adequate sample sizes of nonwhite individuals and individuals with sinus diseases, we oversampled these groups. Sampling fractions included the following: 100% of individuals in the CRS Code group (n = 12 549); 100% of nonwhite and 9.4% of white individuals in the Asthma/Allergy Code group (n = 6093); and 40% of nonwhite and 2% of white individuals in the No Sinus Codes group (n = 5058) (Table 1).

Development of the CRISP population questionnaire

The 'CRISP Questionnaire' was the first to assess both past and current symptoms consistent with the EPOS epidemiologic CRS criteria and is self-administered. It was developed by a panel of experts specializing in otolaryngology, allergy, immunology, primary care, survey research, and epidemiology. Questionnaire items were derived from existing instruments, or items were created *de novo* based on the literature and investigator consensus (8–10). The EPOS criteria require the presence of at least two of four cardinal symptoms of obstruction, anterior/posterior discharge, smell loss, and facial pain/pressure, where at least one symptom is obstruction or discharge, lasting at least 12 weeks (2). We separated pain/pressure and anterior/posterior discharge symptom categories, creating six questions on the following symptoms: obstruction, postnasal drip, posterior nasal drainage, facial pain, facial pressure, and smell loss.

The CRISP Questionnaire first asked whether or not participants had ever had each of the six symptoms in their lifetime that lasted three months or more (yes/no). Affirmative responses were followed by questions on persistence of the symptoms over the past 3 months (never, once in a while, some of the time, most of the time, all of the time). Those respondents who reported one or more symptoms at least most of the time in the last 3 months were instructed to answer an additional 16 questions about the severity and degree of bother associated with each symptom over the past 3 months. These questions were followed by questions on symptoms and diagnoses of known or suspected CRS comorbidities (e.g., allergy, asthma, migraine), CRS treatment history, and sociodemographics.

We pilot-tested the CRISP Questionnaire in 18 otolaryngology clinic patients. Afterward, a research coordinator conducted a cognitive interview to identify aspects of the survey that were unclear and confirmed that questions were understood. The final survey consisted of 94 questions and required approximately 15–20 min to complete (available in online supplemental material).

Patient recruitment

A prenotification letter was mailed to all selected individuals in March 2014, 2 weeks before the CRISP Questionnaire was sent. The questionnaire was mailed with a cover letter and a $1 bill incentive. Those individuals who did not return the questionnaire within 6 weeks were sent a reminder letter and a second copy of the questionnaire. A third and final reminder and questionnaire were sent to nonrespondents 3 months after the initial mailing.

Table 1 Characteristics of source population and patients who responded and did not respond to the baseline survey, CRISP epidemiology study, 2014

Variable	Population eligible for the baseline survey	Population who received baseline survey	Baseline survey responders	Baseline survey nonresponders	Responders vs nonresponders (*P*-value)
Number, total	200 725	23 700	7847	15 853	
Age (years)*, mean (SD)	50.15 (18.45)	49.39 (17.38)	55.04 (16.09)	46.57 (17.33)	<0.0001
Race/ethnicity, *n* (%)					
White	192 356 (95.8)	19 208 (81.0)	7095 (90.4)	12 113 (76.4)	<0.0001
Black	3984 (2.0)	2171 (9.2)	342 (4.4)	1829 (11.5)	
Hispanic	4385 (2.2)	2321 (9.8)	410 (5.2)	1911 (12.1)	
Sex, *n* (%)					
Female	113 592 (56.6)	14 157 (59.7)	4921 (62.7)	9236 (58.3)	<0.0001
Male	87 133 (43.4)	9543 (40.3)	2926 (37.3)	6617 (41.7)	
Medical record groups†, *n* (%)					
CRS Code	13 481 (6.7)	12 549 (53.0)	4800 (61.2)	7749 (48.9)	<0.0001
Asthma/Allergy code	49 917 (24.9)	6093 (25.7)	1843 (23.5)	4250 (26.8)	
No Sinus Codes	137 327 (68.4)	5058 (21.3)	1204 (15.3)	3854 (24.3)	
History of receiving Medical Assistance, *n* (%)	27 494 (13.7)	4427 (18.7)	969 (12.4)	3458 (21.8)	<0.0001
Charlson comorbidity index score, *n* (%)					
0	47 153 (23.5)	4488 (18.9)	851 (10.8)	3637 (22.9)	<0.0001
1	36 229 (18.1)	4802 (20.3)	1244 (15.9)	3558 (22.4)	
2	31 013 (15.4)	3898 (16.5)	1348 (17.2)	2550 (16.1)	
3	25 827 (12.9)	3258 (13.7)	1299 (16.5)	1959 (12.4)	
4+	60 503 (30.1)	7254 (30.6)	3105 (39.6)	4149 (26.2)	

*Age at median date of survey return dates.

†Primary care patients selected based on evidence of CRS, asthma, and allergic conditions in electronic health record: high = two or more ICD-9 codes 471.x or 473.x or CPT codes for sinus surgery, sinus endoscopy or sinus CT; moderate = one ICD-9 code for 471.x or 473.x or two or more ICD-9 codes for asthma (493.x) or allergic rhinitis (477.x); low = does not meet criteria for moderate or high.

Chronic rhinosinusitis classification and symptom subgroups

Operational criteria for current CRS, consistent with the EPOS epidemiological definition, required at least two of the six symptoms most or all of the time in the past 3 months, where at least one of the symptoms was obstruction, anterior nasal discharge, or posterior discharge (postnasal drip). Past CRS was defined in the same manner and as ever occurring for at least 3 months, but not in the last 3 months. Current cases were assigned to one of four subgroups based on frequency of reported symptom combinations as well as on symptoms associated with (CRSwNP) and without (CRSsNP) nasal polyps (11–13). Per EPOS, all individuals had to report obstruction or discharge (anterior or posterior) and were then assigned by what other symptom(s) was reported: (i) smell loss (SL), but no pain or pressure; (ii) pain and/or pressure (PP), but no smell loss; (iii) both smell loss and pain and/or pressure (PPSL); and (iv) obstruction and discharge only, but no smell loss, pain, or pressure (OBS/DC).

Statistical analysis

Selection bias was assessed by comparing respondents and nonrespondents to the CRISP Questionnaire on EHR data that included age, race/ethnicity, sex, history of receiving Medical Assistance (surrogate for socioeconomic status (SES)) (14), the Charlson comorbidity index (15), and EHR sampling strata. Next, prevalence of CRS and CRS symptoms was estimated using SAS Proc SURVEYFREQ (16) to account for sampling fraction and adjust for differential selection using previously published probabilities and participation weights, a standard methodology for referring back to the source population (17, 18).

We conducted unadjusted and adjusted analyses to identify sociodemographic, smoking, and health factors associated with CRS and CRS symptom subgroups. Sociodemographic factors evaluated included sex, race/ethnicity, age, and lifetime Medical Assistance status. Health outcomes included self-reported physician diagnosis of CRS, nasal polyps, asthma, aspirin-intolerant asthma, and hay fever, as well as migraine and fatigue determined by previously validated scales (19). In unadjusted analysis, we used the chi-square test to compare these factors between current CRS and never CRS and across CRS symptom subgroups. In adjusted analysis, we evaluated sociodemographic and health factors separately. For sociodemographic factors, we created separate logistic regression models for current CRS (*vs* never CRS) and each of the CRS symptom subgroups (*vs* never CRS). Each model included sex (male, female), race/ethnicity (white, other), age (linear and quadratic terms to allow for nonlinearity), smoking status (current, former,

never), and Medical Assistance status (yes, no). To identify health outcomes associated with CRS, we used separate logistic models for each health outcome. Each model included a categorical variable for CRS status (never (reference), OBS/DIS, PP, SL, PPSL) as the primary independent variable and the sociodemographic and smoking variables as covariates.

All modeling was performed using SAS Proc SURVEYLOGISTIC procedure, which accounted for the complex sampling design, and utilized sampling and participation weights (17, 18). Weighted analysis balances bias with precision in association estimates; bias is reduced with weighted analysis, but precision is also reduced (larger standard errors leading to larger confidence intervals) (17, 18). One of the sampling weights was an order of magnitude larger than any other (weight = 150), because of the undersampling of white subjects in the 'No Sinus Codes' group. Using this weight severely inflated standard errors, a known consequence of large sampling weights (17–19), so it was truncated to the next largest value (weight = 32), a standard method for dealing with large weights.

Results

The response rate to the mailed questionnaire was 33% (i.e., 7847 of 23 700 patients) (Table 1). Compared to nonrespondents, respondents were significantly more likely to be female, white, have no history of Medical Assistance, have more comorbidities, and have CRS diagnoses codes or sinus procedures in the EHR ($P < 0.0001$).

Prevalence of current CRS, CRS symptoms, and CRS subgroups

After weighting for sampling proportions and participation rates, the estimated prevalence of current CRS in the source population was 11.9% and another 17.0% met criteria for past CRS. The prevalence of current increased from 18 to 59 years to a peak of 15.9% and then declined to a low of 6.8% after 69 years of age ($P < 0.0001$) (Fig. 1).

In order from most to least common, prevalence of current CRS symptoms was as follows: 36.2%, postnasal drip; 27.0%, nasal obstruction (Table 2); 12.6%, facial pressure; 9.4%, loss of smell; 9.1%, facial pain; and 6.5%, nasal discharge. Facial pain and facial pressure were more prevalent than smell loss up to age 59 years. Among those 70 years and older, smell loss was more prevalent (13.6%) than pain (5.0%), pressure (5.8%), and nasal discharge (6.6%).

Of the four symptom subgroups, the OBS/DC subgroup was the most prevalent (4.7%), followed by PP (4.3%), SL (1.8%), and then PPSL (1.2%). PP was more common in women than in men (i.e., women: 5.3%, 95% CI: 4.2–6.5% *vs* men: 2.5%, 95% CI: 1.6–3.4%, and prevalence of PP differed by age, declining sharply after 59 years ($P < 0.0001$). Prevalence of the other subgroups did not differ by sex or age.

Sociodemographic factors associated with current CRS and CRS subgroups

In unadjusted analysis, white race/ethnicity (*vs* nonwhites), younger age, current and former smoking (*vs* never smoker),

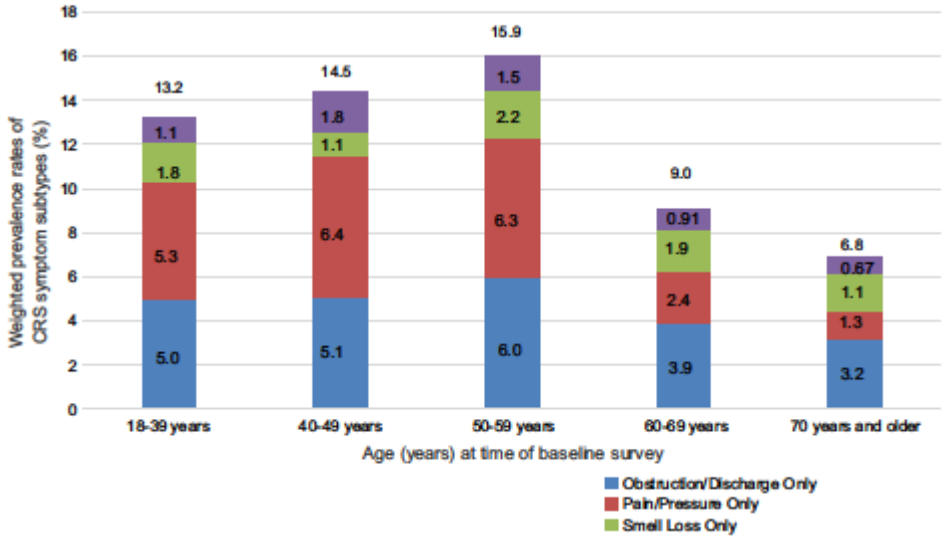

Figure 1 Weighted prevalence (%) of CRS symptom subtypes in a population-based sample by age. Weighted based on sampling and participation rates.

and a history of Medical Assistance were associated with current CRS (*vs* never) ($P < 0.05$). These associations remained in adjusted analysis (Table 3). When CRS subgroups were modeled separately, these associations were no longer significant for some CRS symptom subgroups. Female sex was only associated with PP (OR, 95% CI) (1.81, 1.32–2.49). White race/ethnicity and younger age were each only associated with PP and OBS/DC. Being a current smoker was associated with PP (1.52, 1.03–2.24) and SL (1.8, 1.01–3.11), but former smoking was only associated with SL (1.90, 1.24–2.89). A history of Medical Assistance was only associated with PP (1.78, 1.20–2.64) and PPSL (3.55, 2.08–6.06), groups reporting pain and/or pressure.

Associations of CRS with selected health conditions

In adjusted analysis (Table 4), individuals in each of the CRS subgroups were more likely to report a self-report physician diagnosis of CRS than individuals who did not meet EPOS CRS criteria. Associations were weakest for those with OBS/DC (7.63, 5.44–10.71) and strongest for PPSL (17.67, 10.68–29.24). A similar pattern was observed for associations with self-reported physician diagnosis of nasal polyps, with the weakest associated among those with OBS/DC (3.35, 2.17–5.17) and the strongest for PPSL (6.88, 3.98–11.86). Aspirin-intolerant asthma was associated with all subgroups except for OBS/DC, with the strongest

Table 2 Prevalence* of CRS symptoms† in the source population overall and by sex and age groups

	CRS symptom					
Variable	Obstruction	Nasal discharge	Postnasal drip	Loss of smell	Pain	Pressure
Overall	27.0 (24.5–29.4)	6.5 (5.1–7.8)	36.2 (33.4–39.0)	9.4 (7.7–11.0)	9.1 (7.5–10.7)	12.6 (10.7–14.4)
Sex						
Male	29.0 (24.7–33.2)	6.1 (4.0–8.2)	33.4 (28.8–37.9)	9.7 (7.1–12.3)	5.4 (3.6–7.2)‡	8.8 (6.3–11.2)‡
Female	25.9 (22.9–29.0)	6.7 (4.9–8.4)	37.7 (34.2–41.2)	9.2 (7.1–11.3)	11.0 (8.7–13.2)	14.5 (12.1–17.0)
Age (years) at baseline survey						
<40	30.4 (24.5–36.3)‡	7.1 (4.2–10.0)	33.8 (27.6–40.1)	5.7 (2.9–8.4)	8.2 (5.0–11.3)‡	13.6 (9.3–17.8)‡
40–49	30.8 (24.4–37.1)	4.9 (2.5–7.2)	36.2 (29.3–43.0)	9.4 (5.2–13.7)	15.5 (10.2–20.7)	21.1 (15.3–26.9)
50–59	32.2 (27.1–37.4)	8.9 (5.6–12.1)	37.4 (32.0–42.8)	8.3 (5.4–11.2)	11.2 (7.7–14.7)	15.1 (11.2–19.0)
60–69	20.6 (16.1–25.2)	3.9 (1.7–6.1)	42.6 (36.2–49.0)	10.8 (6.8–14.8)	5.6 (3.0–8.3)	7.4 (4.7–10.2)
70+	19.0 (13.6–24.3)	6.6 (3.1–10.2)	29.2 (22.9–35.4)	13.6 (8.8–18.3)	5.0 (1.9–8.2)	5.8 (2.6–9.0)

*Weighted based on sampling frames and participation rates.
†Symptom reported at least most of the time in the last 3 months.
‡Prevalence differed across characteristic categories ($P < 0.01$).

Table 3 Adjusted associations* (odds ratio, 95% confidence interval) of selected variables with current CRS status among all patients and in symptom subgroups† *vs* no history of CRS ($n = 3842$)

		Current CRS symptom subgroups			
Variable	Current CRS (all) $n = 1873$	OBS/DC $n = 619$	PP $n = 689$	SL $n = 331$	PPSL $n = 234$
Sex					
Female *vs* male	1.14 (0.94–1.37)	0.85 (0.64–1.12)	1.81 (1.32–2.49)	1.22 (0.83–1.80)	0.70 (0.43–1.16)
Race/ethnicity					
Other *vs* white	0.53 (0.40–0.70)	0.41 (0.25–0.67)	0.50 (0.32–0.76)	0.76 (0.42–1.37)	0.85 (0.47–1.52)
Age	0.98 (0.98–0.99)	0.98 (0.97–0.99)	0.96 (0.95–0.98)	1.00 (0.99–1.01)	0.98 (0.96–1.00)
Age-centered squared	1.00 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)
Smoking status					
Current *vs* never	1.31 (1.01–1.70)	0.99 (0.66–1.48)	1.52 (1.03–2.24)	1.78 (1.01–3.11)	1.25 (0.69–2.28)
Former *vs* never	1.24 (1.01–1.52)	0.95 (0.69–1.31)	1.24 (0.90–1.72)	1.90 (1.24–2.89)	1.65 (0.95–2.86)
Medical Assistance					
Ever *vs* never	1.71 (1.30–2.26)	1.45 (0.92–2.29)	1.78 (1.20–2.64)	1.23 (0.69–2.19)	3.55 (2.08–6.06)

OBS/DC = obstruction and discharge only; PP = pain and/or pressure with at least one cardinal symptom (obstruction and/or discharge); SL = smell loss with at least one cardinal symptom; PPSL = pain and/or pressure, smell loss, and at least one cardinal symptom.
*Weighted based on sampling frames and participation rates. Weighted truncated so that the weight of the highest weighted group was weighted at the weight of the next highest weighted subgroup. Adjusted for sex, race/ethnicity, age, age-centered squared, smoking status, Medical Assistance, and age of onset.
†Never: Did not report EPOS CRS symptoms in lifetime; Past: met EPOS CRS symptoms in lifetime but not currently; Current: met EPOS CRS symptoms in the last 3 months.

associations again observed for PPSL (5.82, 2.93–11.57). Each CRS symptom subgroup was associated with asthma and hay fever, with little difference across subgroups. Migraine was associated with all symptom subgroups, particularly for CRS that included pain and/or pressure (PP and PPSL). Odds ratios were more than four times as high in the pain and pressure groups than in CRS without pain or pressure. A similar pattern was observed for severe fatigue.

Discussion

This is the first study in the United States to estimate the prevalence of CRS in a population-based study using the EPOS epidemiologic definition for CRS. We found that CRS is highly a prevalent condition, consistent with studies in similar populations outside the United States that have used EPOS criteria (5). Differential age and sex prevalence patterns by symptom subgroups may be indicative of differences in persistence of disease. These subgroups also differed by risk factors and health outcomes, providing some evidence that CRS symptom subgroups may represent distinct disease processes. This work is an important step toward better understanding of the heterogeneity of sinus symptoms in the general population.

Our findings are consistent with the prevalence estimate for CRS in Europe of 10.9% (5) based on a survey of CRS in adults in 12 European countries. As in other studies, we found a higher prevalence of CRS symptoms in women and a decline in prevalence after age 60 years (3–5, 20). There are two possible interpretations for why cross-sectional prevalence estimates decline with age. The most common explanation is that prevalent cases of CRS are remitting faster than new incident cases are occurring (21). Alternatively, cross-sectional studies represent different age cohorts that may experience differences in exposure to CRS disease mediators that are more intensive for younger age groups than for older age groups. Evidence favors the former explanation. As noted, the age prevalence pattern we observed is consistent with other studies of CRS. Moreover, a number of chronic episodic conditions exhibit a similar age pattern with increasing prevalence to age 40s to 50s and then a decline in prevalence thereafter (22, 23).

Our examination of CRS symptom subgroups revealed that prevalence only differs by age for individuals with pain and pressure and no smell loss. While pain and pressure symptoms appear to drop off after middle age, there is gradual decline with age in CRS with smell loss. Differences by symptom subgroups may reflect differences in persistence and remission patterns. Alternatively, smell loss may persist with age, in part, due to age-related decline in olfactory function that is unrelated to sinus disease (24).

Consistent with prior studies, we found CRS to be associated with migraine (25, 26). Potential mechanisms for this association are the crossover interactions of neurogenic and immunogenic inflammation (26). Alternatively, the association could be due to the overlapping symptoms of these conditions. Migraine is frequently misclassified as sinus headache and frequently accompanied by sinus symptoms (25, 26). In our study, CRS with facial pain and/or pressure has a higher risk of migraine compared to CRS in the absence of these overlapping symptoms. Additionally, the age- and sex-specific prevalence of CRS with pain and pressure mirrored that of migraine; the prevalence of migraine declines after middle age, and prevalence is higher in women than in men (27). Without a clinical exam, it is challenging to parse out comorbid associations from the misclassification of CRS or migraine status.

Smoking was associated with CRS; however, smoking was only predictive of two of the four symptom subgroups. Symptom subgroup differences may be indicative of different

Table 4 Adjusted associations* (odds ratio, 95% confidence interval) of CRS symptom subgroups with selected health conditions†

	Current CRS Symptom Subgroups (vs never)			
Dependent variables	OBS/DC $n = 619$	PP $n = 689$	SL $n = 331$	PPSL $n = 234$
CRS	7.63 (5.44–10.71)	13.23 (9.49–18.43)	15.62 (10.19–23.95)	17.67 (10.68–29.24)
Nasal polyps	3.35 (2.17–5.17)	5.64 (3.80–8.35)	5.24 (3.25–8.43)	6.88 (3.98–11.86)
Asthma	1.59 (1.18–2.14)	1.98 (1.47–2.67)	1.66 (1.08–2.53)	1.76 (1.05–2.96)
Aspirin-intolerant asthma	1.49 (0.82–2.72)	2.74 (1.59–4.69)	2.94 (1.47–5.88)	5.82 (2.93–11.57)
Hay fever	2.60 (1.97–3.42)	2.80 (2.11–3.71)	2.78 (1.88–4.10)	3.29 (2.04–5.31)
Migraine headache	2.73 (1.91–3.92)	10.38 (7.41–14.54)	2.37 (1.33–4.22)	16.87 (8.83–32.21)
Fatigue, moderate (ref minimal)	3.13 (2.13–4.60)	3.18 (1.94–5.22)	3.00 (1.72–5.26)	5.86 (2.09–16.45)
Fatigue, severe (ref minimal)	7.64 (5.00–11.68)	16.81 (10.27–27.52)	8.79 (4.87–15.88)	26.68 (9.43–75.49)

OBS/DC = obstruction and discharge only; PP = pain and/or pressure with at least one cardinal symptom (obstruction and/or discharge); SL = smell loss with at least one cardinal symptom; PPSL = pain and/or pressure, smell loss, and at least one cardinal symptom.

*Weighted based on sampling frames and participation rates. Weighted truncated so that the weight of the highest weighted group was weighted at the weight of the next highest weighted subgroup. Adjusted for sex, race/ethnicity, age, smoking status, and Medical Assistance.

†Self-reported doctor diagnosis for all conditions except for migraine and fatigue. Migraine and fatigue were based on previously validated scales (8, 9).

pathophysiologic mechanisms that may underlie the different symptom profiles. Prior population-based studies of tobacco use and CRS have produced mixed results (3, 5, 20). No prior study has evaluated whether the risk associated with tobacco use differs by symptom profile. Given the differential association of tobacco use with symptom subgroups, conflicting study findings may be due, in part, to differences in the distribution of symptoms in these study populations.

We found an association between a history of receiving Medical Assistance, a surrogate for low family SES, and CRS that was stronger than for all the other variables we examined, including smoking. Notably, this association was strongest for the PPSL group, the group reporting the greatest number of the EPOS symptoms. Similarly, Kilty et al. reported that having education less than high school (*vs* post-secondary education) and having low income (*vs* high) were both associated with higher scores on the Sino-nasal Assessment Questionnaire (SNAQ 11) among patients receiving care for CRS from a rhinology clinic (28). However, a study by Philpott et al. of CRS patients from specialty clinics found no association between CRS and social class, index of multiple deprivation, and education (29). Surrogate measures of SES (i.e., Medical Assistance and income) are not always interchangeable, possibly accounting for conflicting findings. (30) The mechanism of the association between Medical Assistance and CRS severity is unknown, but could be, in part, that Medical Assistance is a surrogate for a number of environmental exposures that differ by SES (31).

The current CRS symptom subgroups were differentially associated with health outcomes, including nasal polyps, aspirin-intolerant asthma, and hay fever, as well as migraine and fatigue. Similar associations have been reported in prior studies of CRS (32–35) but not by symptom status. We found CRS subgroups were most associated with health outcomes when both smell loss and pain and/or pressure were part of the profile, while associations were weakest among CRS profiles without smell loss, pain, or pressure. Differences by subgroup may be evidence of differences in pathophysiology, analogous to differences between CRSwNP and CRSsNP (36). Alternatively, there may be wide variation in the positive predictive value of various symptom groupings within the EPOS criteria to identify patients with true disease. The positive predictive value of the symptom profile for true disease may be lower among individuals with more common symptoms (e.g., obstruction and discharge) than among individuals who report all of the 6 symptoms of CRS and, thus, may result in the relatively weaker associations that were observed for this group.

Among the strengths of this study was that it was conducted in a primary care patient population. Most of what is known about CRS is based on tertiary care studies that often capture only individuals with the most severe symptoms (1). Our study was also the first epidemiological study of CRS in the United States that classified patients based on EPOS epidemiological criteria. Moreover, it was the first population-based study to evaluate associations of selected factors with CRS subgroups. The varying patterns of associations provide some evidence that the heterogeneity in symptom profiles may represent heterogeneity in the underlying pathologic process consistent with. Recent biomarker studies have shown many distinct endotypes of disease (37). Future studies could attempt to cross-reference the CRS symptom subgroups in our study with the endotypes that emerge in the biomarker studies to begin to relate the inflammatory mediators that drive the distinct symptoms combinations.

This study had a few limitations. First, it was not feasible to obtain CTs from the almost 24 000 patients who received a survey. As a result, our prevalence estimates, like all previously published population-based prevalence estimates, were dependent upon symptom reporting. Second, while our response rate was below 40%, our ability to select patients based on electronic health records allowed us to appropriately account for differential participation rates. Third, EPOS criteria do not specify how frequent sinus symptoms have to have occurred over 12 weeks. Criteria is based on duration of symptoms, not frequency, requiring only that symptoms be present for longer than 12 weeks (2). We required that symptoms be present at least 'most of the time' for the last 3 months. By applying a threshold of 'most of the time' it is possible that our findings underestimate the prevalence of CRS, but this is not known because prior studies have not consistently measured frequency of symptom occurrence. Finally, the findings of our study should not be interpreted as an estimate of the prevalence of CRS in the United States, as the study population is not reflective of the US population. However, the GC primary care population is representative of the region's population; thus, our findings provide a valid estimate of the prevalence of CRS in the region studied. (32).

Conclusions

Symptoms compatible with CRS were common but also part of heterogeneous profiles among patients in the general population in central and northeastern Pennsylvania. Prevalence and associations with risk factors and health conditions differed among symptom subgroups. This may be indicative of differences in etiology and natural history that have important implications for targeted disease prevention and management.

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Author contributions

All authors participated in drafting/revision of the manuscript, final approval of the manuscript, and interpretation of findings and agree to be accountable for all aspects of the work. AGH, ASS, BKT, RPS, RCK, and BSS conceived of and designed the study. AGH, AJY, WF, AL, and BSS acquired and analyzed the data.

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Conflicts of interest

The authors have no conflict of interests to report.

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Longitudinal evaluation of clustering of chronic sinonasal and related symptoms using exploratory factor analysis

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Abstract

Background: Sinonasal symptoms are common and can have several underlying causes. When symptoms occur in specified patterns lasting 3 months or more they meet criteria for chronic rhinosinusitis (CRS). Approaches to CRS symptom measurement do not specify how to measure symptoms and treat specified sinonasal symptoms as generally interchangeable, suggesting that such symptoms should cluster on 1 or 2 latent factors.

Methods: We used questionnaire responses to 37 questions on the presence, severity, bother, and frequency of cardinal sinonasal and related symptoms lasting 3 months, from 3535 subjects at 3 time points over 16 months. We completed 5 exploratory factor analyses (EFA) to identify symptom clustering, 1 for each time point and 2 for the differences between adjacent questionnaires. The baseline EFA was used to provide factor scores that were described longitudinally and examined by CRS status.

Results: Five EFAs identified the same 5 factors (blockage and discharge, pain and pressure, asthma and cold/flu symptoms, smell loss, and ear and eye [mainly allergy] symptoms), with clustering determined by symptom frequency, severity, and degree of bother. Responses to individual questions showed changes over time but when combined into factor scores showed less longitudinal change. All symptom factor scores were progressively higher from never to past to current CRS status.

Conclusions: Although the current approaches to symptom characterization in CRS imply a single underlying latent construct, our results suggest that there are at least 3 latent constructs relevant to CRS. Further studies are needed to evaluate whether these clusters have identifiable underlying pathobiologies.

KEYWORDS
chronic rhinosinusitis, exploratory factor analysis, longitudinal, nasal and sinus symptoms, population-based epidemiology

Abbreviations: BMI, body mass index; CRS, chronic rhinosinusitis; CT, computerized tomography; EFA, exploratory factor analyses; EHR, electronic health record; EPOS, European Position Paper on Rhinosinusitis and Nasal Polyps; EPOSa, EPOS epidemiologic definition of CRS based on presence and duration of symptoms only; ICD-9, International Classification of Diseases; IRT, item response theory; KMO, Kaiser-Meyer-Olkin; MANOVA, multivariate analysis of variance; OLS, ordinary least squares; PMM, predictive mean matching; SNOT, Sino-nasal Outcome Test; ULS, unweighted least squares.

1 | INTRODUCTION

Chronic rhinosinusitis (CRS) is an inflammatory condition characterized by sinonasal symptoms, affecting up to 15% of the US population.[1] Various groups have defined 4 cardinal symptoms of the disease which include nasal blockage/congestion, drainage (anterior or posterior combined into single question), smell loss, and facial pain or pressure (combined into single question) lasting at least 12 weeks.[2-5] The European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) has outlined criteria for clinical diagnosis of CRS, requiring subjective symptoms (nasal obstruction or discharge and at least one other symptom) lasting 3 months and objective evidence of inflammation on sinus computerized tomography (CT) scan or endoscopy.[1] Obtaining sinus CT or endoscopy in large-scale population studies is a recognized challenge; therefore, EPOS also advances an epidemiologic definition of CRS based on the presence and duration of symptoms only (which we term $EPOS_s$ CRS, as the definition relying on subjective symptoms). However, EPOS does not specify how to measure symptoms in terms of severity (eg, partial or complete blockage or smell loss and quantity of discharge) or frequency (eg, some, most, or all of the time) during the required 3-month duration.

Current guidelines for CRS primarily divide CRS into one of two primary phenotypes, based on the presence or absence of nasal polyps. However, increasing evidence reveals that CRS is likely much more heterogeneous, with endotypes that are defined by distinct pathophysiologic mechanisms that can be characterized by differences in responses to different treatment options.[6] These endotypes may present with heterogeneous patterns of sinonasal symptoms that could be used in clinical settings to inform targeted treatment strategies. However, to date, the ways in which sinonasal and related symptoms co-occur remain relatively unexplored.[7-9]

Incorporating a large, prospective longitudinal cohort of subjects from Geisinger, an integrated health system, we used exploratory factor analysis (EFA) to assess the existence and structure of latent constructs (as yet unidentified subject attributes driving manifestation of symptoms) of sinonasal and other relevant symptoms. Exploratory factor analyses was applied to symptoms at 3 separate time points over 16 months and the change in symptoms between time points. Prior studies have used EFA applied to CRS symptoms at one point in time, but utilized the Sino-nasal Outcome Test (SNOT) family of questionnaires, designed to assess treatment effectiveness among subjects known to have CRS.[2,10,11] SNOT assesses symptom severity only in a 2-week recall window, so it cannot be used to evaluate compliance with EPOS duration criteria and does not evaluate symptom frequency.[1,11] The questionnaire utilized in this study assessed frequency, bother, and severity of cardinal EPOS symptoms and related and comorbid symptoms (eg, ear, eye, allergy, asthma, headache, fatigue, cold, and flu), to assess a broad range of manifestations potentially associated with sinonasal disease. Understanding how symptoms group together and change over time may allow development of more precise approaches to symptom measurement and help identify biologic rationales for clustered symptoms. To our knowledge, this is the first use of EFA applied to longitudinal information on a broad range of symptoms relevant to sinonasal disease in a sample representative of the general population.

Highlights

- Exploratory factor analysis of 37 symptom questions from three questionnaires obtained from 3535 subjects over 16 months consistently identified five symptom factors.
- The five symptom factors—blockage and discharge, pain and pressure, asthma and cold/flu symptoms, smell loss, and ear and eye (mainly allergy) symptoms—were present in cross-sectional and longitudinal analyses.
- The findings suggest that current approaches to symptom measurement in CRS should be reconsidered, and frequency and severity of symptoms should be incorporated.

2 | METHODS

2.1 | Study population and design

A total of 200 769 Geisinger primary care patients over the age of 18 years were eligible for participation. From these subjects, 23 700 were chosen to receive longitudinal questionnaires in the mail utilizing a previously reported sampling scheme [12,13] which oversampled both racial/ethnic minorities as well as those with higher likelihoods of CRS using *International Classification of Diseases* (ICD-9) and *Current Procedural Terminology* codes in electronic health record (EHR) data.[12,13] Participants who returned the baseline questionnaire were followed up for 16 months. Nonresponders were sent questionnaires 1 or 2 additional times. A total of 7834, 4945, and 4584 subjects returned the baseline (April 2014), 6-month (October 2014), and 16-month (August 2015) questionnaires, respectively, and had answered a sufficient number of the questions of interest as described below.

2.2 | Data collection

The questionnaires included items on the presence, frequency, severity, and bother of a range of symptoms associated with sinonasal disease and comorbid conditions (Table S1).[12-14] Each questionnaire included 37 questions in common with the same response options (how often the symptom occurred in the past 3 months as 1 = never, 2 = once in a while, 3 = some of the time, 4 = most of the time, or 5 = all the time; Table S1). A total of 21 questions were about the presence, severity, and degree of bother of sinonasal symptoms, while the remaining questions assessed the presence of 4 asthma symptoms, 4 allergy symptoms, 3 ear symptoms, and 5 cold/flu symptoms and other related symptoms (Table S1).

2.3 | Analytic variables

EPOS$_6$ criteria were used to classify subjects as current, past, or never CRS based on self-reported current and past symptoms from the baseline questionnaire as previously reported.[13] The questionnaire has been previously described[13] and included sociodemographic items at baseline. Health information such as body mass index (BMI, measured in kg/m^2) was derived from EHR data and linked to questionnaire data.

2.4 | Statistical analysis

2.4.1 | Overview

The goals of the analysis were to identify the latent constructs and their underlying structure, if present, among the 37 questions at each questionnaire time point and then among the change in these symptoms over time from adjacent questionnaires (ie, baseline to 6-month and 6-month to 16-month). The analysis included the 3535 subjects who returned all 3 questionnaires with no more than 5 missing values for the 37 questions for any single questionnaire. We did not want to impute values for subjects with many missing questions as the primary goal of the analysis was to evaluate the underlying latent structure of the patterns of symptom reporting. For subjects with 5 or fewer missing values, which we assumed to be at random, multivariate imputation by chained equations was conducted via the mice R package using the predictive mean matching (PMM) method[15] to impute missing values (approximately 3.5% of values) utilizing only information within each questionnaire. Once data were finalized for each questionnaire, 2 change scores were calculated as the difference between each person's adjacent questionnaires.

2.4.2 | Exploratory factor analysis

Subjects included in the analysis were first compared to subjects not included on demographic, health, and socioeconomic variables to evaluate selection bias. Exploratory factor analyses was next utilized to evaluate the latent constructs and underlying structure of symptom reporting because there were multiple hypotheses and little a priori knowledge of how symptoms might cluster. Implied Pearson's (polychoric) correlations were estimated among the 37 questions for the 3 cross-sectional questionnaires, using the 2-step procedure as implemented by the psych R package.[16] These correlations were then utilized in the EFAs. Pearson's correlation matrices were calculated for each of the 2 change scores as the difference score distribution appeared symmetric and contained more values than practical for polychoric correlations.

2.4.3 | Factor scores and communalities

Each of the 5 EFAs was conducted fitting loadings, estimates, and communalities applying the ordinary (unweighted) least squares (OLS/ULS) procedure to correlations estimated as previously described. We used an oblimin rotation for each EFA to allow factors to be correlated.[16] The number of factors to extract was determined through Cattell's scree test and parallel analysis.[17,18] Factor loadings (values generally ranging from −1 to 1) provide a measure of the strength of the relationship between each question and each of the extracted factors, while the communalities for each question, which range from 0 to 1, are interpreted as the fraction of each question's variability that is explained by the factor model.

Once factor loadings were extracted, item response theory (IRT) scores were estimated for each identified factor for each subject using the polytomous items from each of the questionnaires.[19] These estimated scores were computed as a measure of the strength of each latent factor for each subject. A factor score correlation matrix was first examined to evaluate correlations among the 5 factors. Lasagna plots were examined to visually assess the changes in quintiles of factor scores over time.[20]

We next evaluated factor scores by EPOS$_6$ CRS status groups (current, past, and never). For the 4 factor scores with approximately normal distributions, we used a multivariate analysis of variance (MANOVA) to compare all 4 at once between EPOS$_6$ CRS status groups (MANOVA models what is equivalent to the mean multivariate factor score). The smell loss factor score had a mixed-scale distribution, with many subjects having a value at the lower bound and the remaining individuals distributed relatively uniformly across higher values. Logistic and linear regression models were used to evaluate associations of EPOS$_6$ CRS status with the lower bound factor score and higher scores, respectively. Finally, we evaluated whether the first factor change score, over 6 months, captured more variability in symptoms than the second change score, over 10 months, by comparing EFA communalities using a Wilcoxon signed rank test. We hypothesized that models would explain more variation in symptoms and thus have higher mean communality values, for the first change score because of the shorter duration for change.

2.4.4 | Diagnostics and sensitivity analysis

Extensive diagnostics and sensitivity analyses were completed to confirm the fit and adequacy of EFA models and the sensitivity of results to factoring method and imputation (described in Data S1).

3 | RESULTS

3.1 | Description of study subjects

The 3535 subjects included in the analysis were first compared to the 4312 respondents from the baseline questionnaire excluded from analysis (Table 1). The 2 groups were similar on sex distribution (37.8% vs 36.9% male) and BMI (mean 30.0 vs 30.3 kg/m^2). However, subjects differed on a number of other study variables, including age (mean 57.5 vs 53.2 years), race/ethnicity (94.0% vs 87.5%

TABLE 1 Demographic information of the 4312 subjects who returned the baseline questionnaire but were not included and the 3535 subjects who were included in the analysis

Variable	Excluded from analysis	Included in analysis
Male, n (%)	1591 (36.9)	1335 (37.8)
Age, years, mean (SD)	53.2 (16.8)	57.5 (14.8)
Smoking status		
Never, n (%)	2253 (52.2)	2053 (58.1)
Former, n (%)	1299 (30.1)	1100 (31.1)
Current, n (%)	760 (17.6)	382 (10.8)
Income		
< $25 000, n (%)	1599 (37.1)	1021 (28.9)
$25 000-$50 000, n (%)	1098 (25.5)	970 (27.4)
>$50 000, n (%)	1083 (25.1)	1163 (32.9)
Body mass index, kg/m^2, mean (SD)	30.3 (7.05)	30.0 (6.93)
Education level		
High school, n (%)	1608 (37.3)	1209 (34.2)
Some college, n (%)	1364 (31.6)	979 (27.7)
College graduate, n (%)	977 (22.7)	1171 (33.1)
Race/ethnicity		
White, n (%)	3372 (87.5)	3323 (94)
Black, n (%)	264 (6.1)	78 (2.2)
Hispanic, n (%)	276 (6.4)	134 (3.8)

white), and socioeconomic status (32.9% vs 25.1% earned over $50 000 annually).

Across questionnaires, it was common for symptoms to change by one frequency category, with relatively few subjects changing by 2 or more (eg, results for blockage frequency in Figure 1). For blockage frequency, the majority of those who answered "never" having blockage in the previous 3 months at baseline also reported infrequent blockage at follow-up. Similar patterns of change were observed among subjects who were in other categories of blockage frequency reporting at baseline. This overall pattern of symptom reporting across questionnaires was evident for other symptom questions as well (results not shown).

3.2 | Cross-sectional EFAs

For each of the 3 cross-sectional EFAs, scree plots supported the extraction of 5 factors (Figures S1 to S3). Parallel analysis suggested the retention of 5 factors for baseline and 6-month questionnaires and 6 factors for the 16-month follow-up. For ease of comparability, 5 factors were extracted from each of the questionnaires. Each of the structures and the interpretation of the 5 factors in these 3 EFAs were similar: one factor each for symptoms of blockage and discharge, pain and pressure (including headache), asthma and cold/flu symptoms, ear and eye, and smell loss (Table 2 for baseline EFA, other 2 cross-sectional EFAs in Tables S2 and S3). Factor loadings (the degree to which specific question was related to latent factor) were consistent across all questionnaires (Tables 2 and S2 and S3). Most observed communalities were high, indicating that the factor models well-represented questions included in the analysis (Tables 2 and S2 and S3). A few low communalities were observed (eg, bad breath [0.26], fever [0.34], cold/flu symptoms [0.37], and fatigue [0.39]), suggesting that the model did not account for much of the variability in these symptoms.

3.3 | Longitudinal difference EFAs

The 2 longitudinal difference EFAs also supported 5 factor models (scree plots in Figures S4 and S5). Symptoms identified to load on single factors in the difference analyses indicated that these symptoms changed together and in the same direction over time. Notably, both difference EFAs yielded nearly identical factors and structures

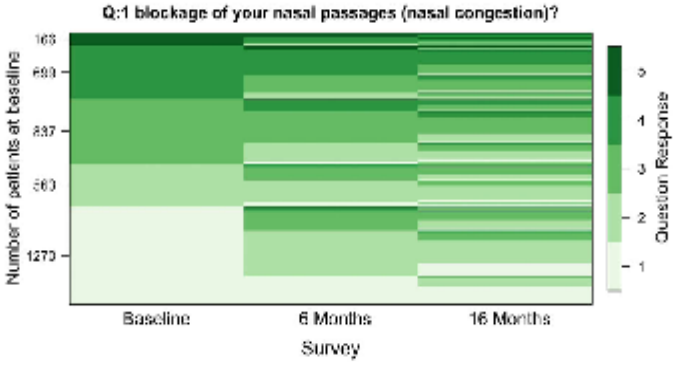

FIGURE 1 Lasagna plot displaying the proportion of individuals with each given response to the question "On average, how often in the past 3 months have you had postnasal drip?" at baseline and 6 months and 16 months later (1 = never, 2 = once in a while, 3 = some of the time, 4 = most of the time, 5 = all the time). Y-axis values indicate the number of subjects with specific responses at baseline [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Factor loadings and symptom communalities from the exploratory factor analysis (EFA)[a] of 37 questions about the presence, frequency, and severity of sinonasal and related symptoms on the baseline questionnaire from 3535 subjects

		Factor					
#	Item label	1	2	3	4	5	Communalities
1	Blockage	0.65					0.80
2	Discharge discolored	0.49					0.61
3	PND	0.84					0.78
4	Smell loss				0.95		0.89
5	Facial pain		0.83				0.85
6	Facial pressure		0.76				0.87
7	Blockage both sides	0.58					0.72
8	Blockage complete	0.55					0.73
9	Blockage bothered	0.61					0.81
10	Discharge a lot	0.86					0.84
11	Blow nose 10x daily	0.82					0.76
12	Discharge bothered	0.84					0.84
13	Cough lie down	0.72					0.73
14	Lump in throat	0.69					0.73
15	PND bothered	0.84					0.85
16	Smell loss complete				0.97		0.95
17	Smell loss bothered				0.92		0.91
18	Facial pain 5+		0.83				0.90
19	Facial pain bothered		0.84				0.91
20	Facial pressure severe		0.77				0.86
21	Facial pressure bothered		0.78				0.90
22	Headaches		0.67				0.48
23	Fever			0.43			0.34
24	Coughing	0.46		0.50			0.53
25	Bad breath						0.26
26	Fatigue						0.39
27	Nasal itching					0.56	0.53
28	Sneezing	0.31				0.54	0.51
29	Eye itching					0.72	0.62
30	Eye tearing					0.60	0.49
31	Ear fullness		0.35			0.54	0.62
32	Ear pain		0.51			0.49	0.65
33	Ear pressure		0.47			0.46	0.63
34	Wheezing			0.80			0.66
35	Chest tightness			0.85			0.78
36	Shortness of breath			0.82			0.68
37	Cold/flu symptoms			0.44			0.37

[a]The EFA was fit using ordinary least squares(OLS) and an oblimin rotation. Loadings less than 0.3 were omitted for readability. Communalities represent the fraction of each symptom's variability that was captured by the utilized 5 factor models.

(Tables 3 and S4) to the cross-sectional EFAs. As expected, given the shorter duration for change, the baseline to 6-month difference EFA had a significantly greater average communality than did the 6-month to 16-month difference EFA (*P*-value = .002 from Wilcoxon signed rank test; Table S5).

3.4 | Factor scores

Using the baseline model to estimate factor scores within individuals at baseline, correlations among the 5 factor scores ranged from 0.30 to 0.64. The highest interfactor correlations were observed between

TABLE 3 Factor loadings and symptom communalities from the exploratory factor analysis (EFA)[a] of change in responses from the 6- to 16-month questionnaire on 37 questions about the presence, frequency, and severity of sinonasal and related symptoms from 3535 subjects

		Factor					
#	Item Label	1	2	3	4	5	Communalities
1	Blockage	0.46					0.30
2	Discharge discolored	0.32					0.19
3	PND	0.49					0.28
4	Smell loss					0.68	0.47
5	Facial pain		0.66				0.47
6	Facial pressure		0.59				0.41
7	Blockage both sides	0.43					0.28
8	Blockage complete	0.34					0.23
9	Blockage bothered	0.52					0.40
10	Discharge a lot	0.72					0.50
11	Blow nose 10x daily	0.66					0.43
12	Discharge bothered	0.75					0.54
13	Cough lie down	0.34			0.33		0.29
14	Lump in throat	0.36					0.27
15	PND bothered	0.57					0.40
16	Smell loss complete					0.84	0.69
17	Smell loss bothered					0.68	0.48
18	Facial pain 5+		0.78				0.60
19	Facial pain bothered		0.79				0.63
20	Facial pressure severe		0.65				0.44
21	Facial pressure bothered		0.72				0.54
22	Headaches						0.14
23	Fever						0.10
24	Coughing				0.42		0.29
25	Bad breath						0.12
26	Fatigue						0.12
27	Nasal itching			0.35			0.19
28	Sneezing			0.38			0.25
29	Eye itching			0.50			0.29
30	Eye tearing			0.51			0.30
31	Ear fullness			0.64			0.41
32	Ear pain			0.53			0.33
33	Ear pressure			0.63			0.39
34	Wheezing				0.58		0.33
35	Chest tightness				0.64		0.40
36	Shortness of breath				0.60		0.37
37	Cold/flu symptoms				0.35		0.24

[a]EFA was fit using ordinary least squares (OLS) and an oblimin rotation. Loadings less than 0.3 were omitted for readability. Communalities represent the fraction of each symptom's variability that was captured by the utilized 5 factor models.

the blockage and discharge factor with the pain and pressure factor ($\rho = .64$) and the smell loss factor ($\rho = .61$; Figure S6). There was a significant difference (*P*-value <.001) in mean factor scores for factors 1, 2, 3, and 5 between $EPOS_s$ CRS groups (current, past, and never; Figure 2 for factor 1). We observed factor scores were higher, in descending order, for current, past, then never CRS groups. Examination of factor scores across questionnaires (categorized values in Figure 3 for factor 1) showed that there was change in factor scores over time. Logistic and linear regression models revealed that $EPOS_s$ CRS status was positively associated with smell loss (factor 4) scores. Current and past $EPOS_s$ CRS at baseline (vs never) were associated with a much lower odds of having low factor scores (odds

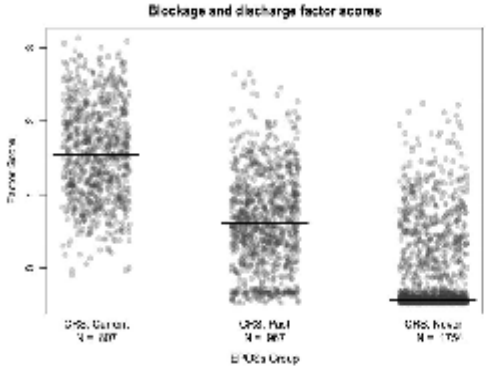

FIGURE 2 Factor 1 (blockage and discharge) scores by EPOS$_6$ chronic rhinosinusitis (CRS) groups (current, past, and never) at baseline. The number of subjects in each group is indicated. Factor scores were estimated by the item response theory (IRT) method. The X-axis was jittered to improve readability

ratios [95% CI] = 0.05 [0.04, 0.06] and 0.15 [0.12, 0.18], respectively). For those above the lower bound score, subjects with current and past EPOS$_6$ CRS at baseline (vs never) had higher factor scores, with a mean (95% CI) factor 4 score of 0.48 (0.35, 0.60) and 0.22 (0.10, 0.34), respectively.

4 | DISCUSSION

Exploratory factor analyses was used to better understand the existence and structure of latent constructs underlying symptoms which have been traditionally categorized as major and minor CRS symptoms[21] as well as symptoms associated with CRS comorbidities. Notably, this was performed in a general population representative sample utilizing both cross-sectional symptom questionnaires and changes in symptom responses over time. The analysis of sinonasal, asthma, headache, cold/flu, allergy, and ear symptoms identified 5 factors (ie, symptom clusters representing latent constructs) that were similar in all 3 cross-sectional and 2 difference analyses, despite some change in symptoms over time. The 5 factors were blockage and discharge, pain and pressure, asthma and cold/flu, smell loss, and ear and eye symptoms (mainly allergy). All 5 factor scores were highest in subjects who met EPOS$_6$ current CRS criteria and lowest in those who met EPOS$_6$ never CRS criteria. Understanding how symptoms cluster within and across questionnaires can provide useful information that can aid clinical practice, inform symptom measurement in CRS, and lead to hypotheses about the pathobiology underlying these clusters.

In EPOS guidelines, the 6 symptoms we measured are reduced to 4 as anterior and posterior discharge and pain and pressure are combined. European Position Paper on Rhinosinusitis and Nasal Polyps considers these 4 cardinal symptoms to be mainly interchangeable, with one required symptom (one of the 3 blockage or discharge symptoms) and one other symptom to meet EPOS criteria. If there was an underlying construct of CRS that could be measured with the cardinal symptoms, the EPOS criteria suggest symptoms should only load on 1 or 2 factors. We subjected a larger group of 37 symptom questions, encompassing common sinonasal and comorbid condition symptoms, and expanded to evaluate how severity, bother, or frequency influenced clustering. The results suggested that frequency, severity, and bother were all important to clustering of symptoms within factors. European Position Paper on Rhinosinusitis and Nasal Polyps allows either blockage or discharge to be a separate required symptom, but we found that all 12 blockage and discharge questions loaded on a single factor, suggesting these symptoms do not occur independently of one another. We found that the 37 symptoms identified 5 factors and the 6 EPOS CRS symptoms clustered in 3 factors (ie, nasal blockage and discharge,

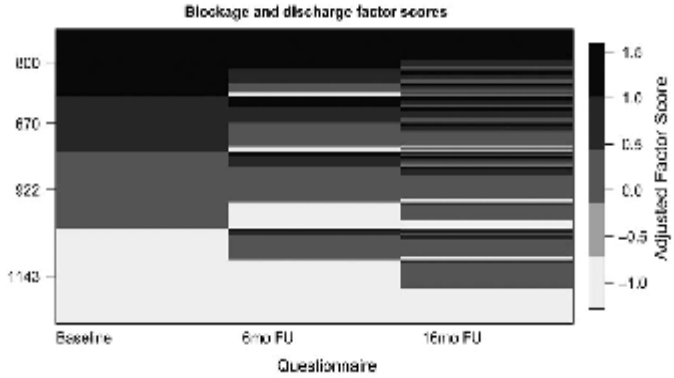

FIGURE 3 Continuous factor scores categorized to show longitudinal change across questionnaires for factor 1 (blockage and discharge). Factor scores were categorized as: factor score <−0.4 were assigned values of −1; between −0.4 and 0.6, assigned 0; between 0.6 and 1.2, assigned 1; and > 1.2, assigned 1.3. The Y-axis labels indicate the number of subjects at baseline in each adjusted factor score group. Factor scores were estimated by the item response theory (IRT) method

facial pain and pressure, and smell loss), in all 5 EFAs. Most questionnaire responses were well-represented by the observed factor models as indicated by relatively high communality values.

While there was some longitudinal change in symptom reporting, large transitions (2 or more steps on the Likert scale) were not very common. However, this could still result in large differences in proportions meeting EPOS$_e$ criteria for CRS over time and lead to misclassification of CRS status when symptoms are assessed at cross section. For example, we have previously reported that, among subjects who met EPOS$_e$ current CRS at baseline, almost half did not meet criteria for current CRS 6 months later.[24] The latent constructs, however, were stable over time. Prevalence estimates around the world range from 5.5% to 15%,[2,3,24] and differences may be partially attributable to differences in when and how EPOS$_e$ criteria are operationalized (ie, symptoms assessed via Likert scale vs a binary measure of symptom presence or absence), as some methods may be more or less sensitive to the variability of symptoms over time. A standard approach to measuring symptoms in epidemiologic studies using EPOS$_e$ criteria is required to understand differences across studies and populations.

There has been increasing recognition of the heterogeneity of CRS with a focus on multiple groups of endotypes.[4,25] An important question is whether the clustering of symptoms we observed represents one or more endotypes with distinct underlying pathobiologic processes or anatomic relationships. In a prior study, we found that similar distinct sinonasal symptom patterns within individuals meeting EPOS$_e$ differed by age, sex, selected risk factors, and health outcomes, providing some evidence that CRS symptom subgroups may represent distinct disease processes.[13] The ability to use symptoms to identify subtypes of CRS that might differ by inflammatory processes, location of sinus opacification, and comorbidities, for example, has important implications for targeted treatment of the disease.

The consistency of the 5 factors in all 5 EFA models, despite the presence of some longitudinal change in symptoms, also provides some evidence that these 5 factors may each have an underlying pathobiology. EFA theory hypothesizes that there are real underlying mechanisms, including common pathobiology or reporting phenomena, which manifests in clustering of symptoms into observed factors. If this hypothesis was correct, we would expect factor composition to be invariant to time (ie, within questionnaires and no seasonality) and to see symptoms cluster over time according to these same factors. Our observed results supported both of these expectations.

Analysis of multidimensional mean factor scores showed that EPOS$_e$ current CRS had the highest factor scores, followed by the past CRS group (*P*-values <.01). This result is unsurprising as the CRS groups here were determined by the EPOS$_e$ definition, which itself is based on many of the symptoms in the factors; however, the EFA included many questions beyond those used to define EPOS$_e$ CRS status. The factor scores comprised of eye, ear, asthma, cold/flu, and headache symptoms may represent the common co-occurrence of allergy, asthma, and headache disorders, for example, among patients with sinonasal disease.

While there has been some prior work on CRS symptom factors at a single point in time with the SNOT-20 and SNOT-22 questionnaires, prior work on factors using longitudinal information on symptoms has generally focused on the impact of treatment.[10,26] The SNOT questionnaires using 20 or 22 Likert-scale questions ask the participants to consider physical, functional, and emotional symptoms in the previous 2 weeks.[27,28] SNOT was designed to provide a single measure of patient quality of life and CRS-related symptom severity and implicitly suggesting that the combined questions provide information regarding a single CRS construct or factor.[10] However, prior studies of SNOT-20 or 22 found 4 or 5 factors such as rhinologic symptoms, extranasal rhinologic symptoms, ear and facial symptoms, psychological dysfunction, and sleep dysfunction implying a variety of unobserved underlying factors.[10,27,29] The difference in symptom duration between SNOT and our questionnaire might explain the absence of latent constructs within the rhinologic symptoms in SNOT.

We observed differences between subjects included and excluded from the analysis. Included subjects were more likely to be white, more highly educated, and have higher incomes. This may have resulted in selection bias that could have influenced the results. In addition, there is the potential of same source bias impacting results by which some individuals report in a systemic manner (eg, always or never reporting symptoms, or more likely to report symptoms located near each other on the questionnaire with the same response item). Finally, while we found strong evidence of clustering among 37 symptoms within visits and over time, the ultimate utility of the findings will be in whether these 5 factors identify unique CRS subgroups (new approaches to phenotypes, or combined with molecular measurements into endotypes) that predict natural history, response to treatment, or long-term outcomes.

5 | CONCLUSIONS

In an analysis of 37 sinonasal, allergy, ear, asthma, headache, and cold/flu symptoms, we identified 5 underlying factors—blockage and discharge, pain and pressure, asthma and cold/flu, ear and eye, and smell loss—that were very consistent in 3 cross-sectional and 2 longitudinal change EFAs. Questions assessed the presence, severity, bother, and frequency of all 37 symptoms. Frequency, severity, and degree of bother were each important to clustering of symptoms within factors, and this clustering within factors was stable over time. The findings have implications for how to measure sinonasal symptoms in epidemiologic studies of CRS and possibly in the clinical setting too (eg, EPOS criteria). Future consideration should be given to whether and how to incorporate frequency and severity into symptom measurement to optimize diagnosis and care for patients with nasal and sinus symptoms.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

AUTHOR CONTRIBUTIONS

Matthew Cole performed the analysis and wrote the first draft of the manuscript. Karen Bandeen-Roche supervised the data analysis, helped in the interpretation of the results, and edited several drafts of the manuscript. Annemarie G. Hirsch participated in questionnaire design, data collection, interpretation of results, and editing of the manuscript. Jordan Kuiper participated in interpretation of results and editing of the manuscript. Agnes S. Sundaresan participated in questionnaire design, data collection, interpretation of results, and editing of the manuscript. Bruce K. Tan, Robert P. Schleimer, and Robert C. Kern each participated in study design, securing of extramural funding, questionnaire design, interpretation of results, and editing of the manuscript. Brian S. Schwartz participated in study design, securing of extramural funding, supervision of all phases of the study, directing data analysis, interpretation of results, and editing of the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Cole M, Bandeen-Roche K, Hirsch AG, et al. Longitudinal evaluation of clustering of chronic sinonasal and related symptoms using exploratory factor analysis. *Allergy*. 2018;73:1715–1723. https://doi.org/10.1111/all.13470

Study Application (Version 1.15)

1.0 General Information

*Please enter the full title of your study:		
Validation of a Questionnaire to Identify Patients with Chronic Rhinosinusitis		
***Please enter a short descriptor that you would like to use to reference the study:**		
CRS CT Validation * This descriptor allows you and other study team members to quickly identify the study. This would be the acronym/ sponsor protocol and/or abbreviated study title.		
Please identify the Research Type?		
Ear/Nose Throat Conditions		

2.0 Add Department(s)

2.1 List departments associated with this study:

Primary Dept?	Department Name
◉	**GMC** - Center for Health Research

3.0 Assign key study personnel(KSP) access to the study

3.1 *Please add a Principal Investigator for the study:

Schwartz, Brian S, MD, MS

3.2 If applicable, please select the Research Staff personnel:

A) Additional Investigators

Hirsch, Annemarie, Ph.D.
Co-Investigator/ Sub-Investigator
Sundaresan, Agnes S, MD
Co-Investigator/ Sub-Investigator

B) Research Support Staff

Coffman, Vanessa
Collaborator
Cole, Matthew
Collaborator
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Biostatistician
Dewalle, Joseph J, BS
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Kuiper, Jordan
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Mercer, Dione G
Project Manager
Mowery, Jacob, B.A.
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Biostatistician
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Pollak, Johnathan, MPP
Biostatistician
Tan, Bruce K
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Young, Amanda J, MS
Biostatistician

3.3 *Please add a Study Contact:

Mercer, Dione G
Schwartz, Brian S, MD, MS

The Study Contact(s) will receive all important system notifications along with the Principal Investigator. (e.g. The project contact(s) are typically either the Study Coordinator or the Principal Investigator themselves).

3.4 If applicable, please select the Designated Department Approval(s):

Add the name of the individual authorized to approve and sign off on this protocol from your Department (e.g. the Department Chair or Dean).

3.5 If applicable, please select the Administrative Assistant(s):

Administrative Assistant Note

4.0 Basic Review Questions

4.1 Are you reporting an emergency use of an investigational drug or device?

○ Yes ◉ No

4.2 Does the study involve research that may be deemed Exempt? (Prior to checking, please be sure to review the exemption categories outlined in the Help Link)

○ Yes ◉ No

4.3

Does the study ONLY involve use of existing medical records, databases, specimens, etc. (i.e. already on the shelf or collected on or before submission of the study to the IRB)?

○ Yes ◉ No

Please note: Only check YES if the proposed research only involves use of existing (already on the shelf or collected at the time of IRB submission) patient-related information from medical records (both electronic and paper), databases and/or discarded specimens.

Please note: Do not check YES if the study involves prospective data or specimen collection.

4.4 Does the proposed research examine nursing processes, practices, or nursing theory? (ie, studies regarding interventions, measures, outcomes)

○ Yes ◉ No

NOTE: Nurse-initiated research (nurse serving as PI or Co--I) is reviewed and tracking through the Nursing Research Council (NRC).

Designated NRC Unique Tracking Number:

☐ Research proposals are acknowledged by NRC when conducted by a nurse with earned doctorate
☐ Research proposals require NRC approval when conducted by a nurse without an earned doctorate.

5.0 Initial Review Application: Health and Biological Sciences

5.1 Geisinger believes research is important and should be visible to the community and patients. After approval of your study, information about your research study will be included in "Find a Study" on Geisinger's public website. "Find a Study" includes specific contact information for direction of questions or interest in the study. Please enter the following information that should be included for the study:

Enter name of study contact for "Find a Study":

Dione Mercer

Enter study contact email for "Find a Study":

dgmercer@geisinger.edu

Enter study contact phone number for "Find a Study":

570-214-9934

Describe the study's target population:

Geisinger patients who participated in previous CRS survey study.

Select the gender of the target population:

○ Male
○ Female
◉ Both

Describe the target age range of the study:

18-89

Please add any other information or additional comments that you would like to include about this study on "Find a Study":

We are no longer recruiting for this study.

5.2 Location of the Research

☑ Geisinger facility
☐ Non-Geisinger facility

Name of facility:

Please attach a letter of support from the non-Geisinger facility.

5.3 Please summarize the proposed study using lay (non-technical) language that can be easily understood by the general public.

PLEASE NOTE: The summary will also be used to describe your study in "Find a Study" on geisinger.org.

This is substudy of a larger epidemiologic study to address the gaps in understanding Chronic Rhinosinusitis (CRS) prevalence, incidence, and natural history, and to evaluate disease burden, environmental risk factors, and utilization of health care. This substudy is a prospective study to validate a CRS questionnaire. We will be obtaining Computed Tomography (CT) images to compare to responses to the CRS questionnaire. We will then obtain sinus CT scans from 600 patients who complete the questionnaire. By documenting the performance of the questionnaire in this subset of patients with a sinus CT, we will determine whether the questionnaire is a valid method of identifying patients with CRS.

5.4 Identify how this research study is funded.

View Details	Sponsor Name	Sponsor Type
⊟	NIH	Federal

Sponsor Name:	NIH
Sponsor Type:	Federal
Sponsor Role:	Funding
Grant/Contract Number:	
Is Institution the Primary Grant Holder:	No

PLEASE NOTE: If there is no funding for the study or if the study is departmentally funded, please select "Geisinger Clinic" as the Sponsor. Regardless of funding, there is a cost to conducting all research, e.g. personnel time; therefore, the clinical department (Geisinger) is supporting the research activity by paying the salary of staff who spend time working on it.

If the study has received external or internal (Geisinger Research Fund) grant funding, a copy of the grant application must be uploaded with the submission.

5.5 Indicate the level of risk associated with this study.

○ Minimal Risk
◉ Greater Than Minimal Risk

Describe all reasonably expected risks, harms, and/or discomforts that may apply to research. Discuss severity and likelihood of occurrence. *Consider the range of risks, including physical psychological, social, legal, and economic.*

Paients will be asked to come into the clinic for a CT scan of their sinuses. The radiation dose associated with the CT scan is no greater risk than spending a week out in the hot July sun. Some patients may also be uncomfortable in the confined space of the CT scanner.

Describe how risks, harms and/or discomforts will be minimized. If testing will be performed to identify individuals who may be at increased risk (e.g., pregnant women, individuals with HIV/AIDS, depressive disorders, etc.), address timing and method of testing: include how positive tests will be handled.

We have developed a low dose CT scan for this project, which is significantly lower than the standard clinical dose scan (see attached documentation from the Radiation Safety Committee), thus greatly reducing the radiation exposure. The scan itself will only take a few minutes, thus patients concerned about spending a lengthy time in the scanner will be minimized.

If the study involves greater than minimal risk, provisions for safety monitoring are required to protect participants. Please indicate below the plan for monitoring safety in this study:

- ☐ Data Safety Monitoring Board (DSMB)
- ☐ Data Safety Monitoring Committee (DSMC)
- ☐ PI and Study Staff
- ☑ Other

If Other, please define:

The Radiation Safety Committee has reviewed and approved this project. Please see attached documentation.

A data safety monitoring plan is also required, below are the monitoring details.

1. Monitoring of Safety and Confidentiality: The monitoring will be the responsibility of the PI, Co-I with assistance from the Project Manager. All patient data collected for the study will be stored in locked file cabinets/offices and/or secure password protected computers in shared folders only accessible by approved study staff. Study IDs are assigned to patient data in order to protect confidentiality. A access study database will track study participation and opt-outs. The informed consent process will be obtained prior to proceeding with the CT scans. The PM will periodically review the consent forms throughout the study to assess completeness and correctness. All data collection will follow the approved protocol, as attached to this IRB application. All CT scans will be assigned a study ID and thus are deidentified for the collaborators who will be reviewing the images at the University of Chicago and Johns Hopkins.
2. Plan for Data Management: The approved study team Project Manager, Research assistant and Intern with assistance from the Call Center and Radiation Technicians will be responsible for the collection and storage of the data with oversight from the PI and Co-I. The EHR data as well as all other data collected as part of this study is stored on a password protected computer in a shared study folder only accessible to approved study staff. Paper copies of consents will be stored in a locked file cabinet accessible only by approved study staff. The study tracking database is password protected with access only to approved study staff. intermittent data reviews will be done by the Project Manager of the study, and reported back to the PI and Co-I during the weekly study team meetings. Analysis of data will be performed by approved data analysts and biostatisticians on the study.
3. Protocol Deviations/Adverse Events: Any protocol deviation or adverse event related to the study will immediately be reported to the PI and Co-I and then appropriately reported to the Office of Research Compliance and IRB.

5.6 Please identify any benefits that may be reasonably expected to result from the research, either to the subject(s) or to society at large.

One of our goals of this reasearch project is to develop a survey tool that well characterizes CRS patients, in hopes that in the future patients would not have to have a CT scan or other clinical invasive procedures to confirm a CRS diagnosis.

Payment to subjects is not considered a benefit in the risk benefit assessment.

5.7 Does your study involve any of the following?

- ☐ Drugs, Biologics or Dietary Supplements
- ☐ Device(s)
- ☑ Not applicable

5.8 Human Subjects - a living individual about whom an investigator (whether professional or student) conducting research obtains: (1) Data through intervention or interaction with the individual, or (2) Identifiable private information.

How many subjects do you plan to enroll:

675

How many people do you estimate that will go through the consent process (but not necessarily enroll) to get the planned "enrolled" subjects?

3500

All records and/or subjects who are reviewed and/or approached for this research study should be included toward the total number of subjects even if they have no further participation in the study (i.e. drop out, screen out, choose not to participate).

Indicate the total number of subjects to be enrolled across all sites:

Is this a multi-site study?

○ Yes ◉ No

If yes, are you the lead researcher of the multi-site study?

○ Yes ○ No

If yes, please include the following specific details in the protocol on how the following will be managed or outline specific details in the box below:

- **Unanticipated problems involving risk to participants or others**
- **Interim results**
- **Protocol modifications**

Describe populations to be excluded from the research. *Please describe procedures to ensure equitable selection of subjects*

Pregnant women will be excluded from this research. The phone recruitment script (see attached) has specific questions about pregnacy which would automatically exlude them from participating in the CT scan.

Will vulnerable populations be targeted in the research?*(check all that apply):*

- ☐ Minors (< 18 years of age)
- ☐ Decisionally Impaired
- ☐ Students
- ☐ Geisinger employees
- ☐ Pregnant Women/Fetuses)

☐ Prisoners
☐ Other

If Other, please specify:

If vulnerable populations are included, please provide a description of the additional safeguards that are used to protect the vulnerable population's rights and welfare.

Provide rationale and justification for the inclusion of each special vulnerable population in the research. Please note "vulnerable" populations require special consideration by the federal regulatory agencies and by the IRB.

N/A

Age Range

☐ 0-6 years
☐ 7-17 years
☑ 18+ years

5.9 Please upload all proposed recruitment materials, e.g. advertisements, bulletin board notices, telephone scripts, and recruitment letters for all planned types of media (printed, radio, electronic, TV, or Internet). Each recruitment item must be labeled for its particular use and MUST have a footer containing an identifier, version number, and date. Recruitment flyers must be provided in the final format for approval.

5.10 Please check all applicable recruitment forms.

☐ Ad (print)
☐ Ad (radio-provide script, then tape)
☐ Ad (TV-provide script, then video)
☐ Brochure
☐ E-mail notice
☐ Flyer
☐ Information sheets (before study)
☐ Information sheets (on study)
☐ Internet
☐ Mass Mailing
☐ No recruitment materials will be used
☐ Physician to Physician Letter
☐ Physician referral
☐ Records (e.g. medical, employment, school)
☑ Recruitment Script (to aid in consent process)
☐ Registry or Bank
☐ Student Subject Pool
☑ Subject Letter
☑ Telephone script/guidance
☐ Other

If Other, please describe:

5.11 Initial Contact

Explain who will approach subjects to take part in the research and what will be done to protect the subject's privacy in this process:

Based on survey responses from study 2013-0322 a subset of patients will be identified as qualifying for a CT scan. These study subjects will be sent a letter consent packet and short CRS symptom survey (subset of questions from previous surveys from study 2013-0322) asking them to participate in the CT portion of the study. If they mail back the consent form, a memeber of the call center will call them and explain the study in more detail and schedule an appointment for a CT scan. The call center will also contact those patients that have not mailed back a consent and ask them if they would be interested in participating, if the participant agrees another consent packet will be mailed to their home and upon recieving the signed consent the call center will contact them to schedule the CT scan. Please see attached work flow for the call/consent process, including the CT visit.

Initial contact of subjects identified through records search must be made by the official holder of the record, i.e. primary care physician, therapist, and public school official.

5.12 Screening and Recruitment

Are you requesting waiver of HIPAA authorization for recruitment purposes?

(•) Yes ( ) No

*If **yes**, please complete the Partial Waiver of Authorization for Recruitment.*

5.13 Does the study require the use of tests, procedures, clinic space, clinic visits, professional fees, lab services, pharmacy services or hospital services in order to answer the research question(s)?

(•) Yes ( ) No

If yes, a copy of the study schema and billing determination prepared by the Office of Sponsored Programs (OSP) and approved by Office of Research Compliance (ORC) must be uploaded with the submission.

5.14 Compensation and costs of participation

Will subjects receive any compensation or inducements before, during, or after participation in the study (i.e. money, gifts, gift certificates)?

(•) Yes ( ) No

If, yes, please check all the appropriate types and reason for the reimbursement or inducement.

[x] Monetary
[ ] Non-Monetary
[ ] Time

If monetary, please provide the amount and timing of payments to participants.

$60 gift card mailed to participant 4-6weeks after completion of CT scan.

If non-monetary, please describe:

If other, please define:

5.15 How will informed consent/assent be obtained for the study? *Please check one of the following*

(•) Written Consent
( ) Waiver of written documentation of consent (Verbal consent from subjects will be obtained)

○ Waiver of consent (no consent from subject will be obtained.)

5.16 Confidentiality of Data

Explain how information is handled, including storage, security measures (as necessary), and who will have access to the information. Include details for both electronic and "paper" copy records.

Data will be accessible by IRB approved study staff only. The study team will not receive MRN as part of this project. Data will be accessible by IRB approved study staff only. The study team will not receive MRNs as part of this study, all data will use a study ID in place of MRN. The data broker in the Biostats Core will hold a link to the MRN in the event that the study would need to go back to request additional EHR data on the study cohort.

CT scans will be de-identified by the Technician at time of scan with a random number. The CT images will be sent to the CHR study team via an IT/ISO approved transport method. Once the CT scan images are received at CHR a study team member will verify deidentification and upload the images to an IT/ISO approved FTP site where study collaborators from Northwestern university and Johns Hopkins (2 seperate FTP sites) will download for interpretation. Only approved study staff at CHR will hold the link between CT images and EHR data of the participant.

Explain if any personal or sensitive information that could be potentially damaging to participants (e.g., relating to illegal behaviors, alcohol or drug use, sexual attitudes, mental health, etc.) will be collected.

No sensitive information as described above will be collected for this study.

Please provide details regarding retention of research records (including identifiable data) at the end of the study. For instance, how long and where will the research records and data be maintained.

Data will be kept indefinitely for use in future IRB approved research studies

Please check all the PHI elements that will be received by the study team:

- ☑ Names (first name, last name, or initials)
- ☑ Geographic subdivisions smaller than a state
- ☑ Dates
- ☑ Telephone numbers
- ☐ Fax numbers
- ☐ E-mail addresses
- ☐ Social security numbers
- ☐ Medical record numbers
- ☐ Health plan beneficiary numbers
- ☐ Account numbers
- ☐ Certificate/license numbers
- ☐ Vehicle identifiers and serial numbers, including license plate numbers
- ☐ Device identifiers and serial numbers
- ☐ Web addresses – universal resource locators ("URLs")
- ☐ Internet protocol ("IP") address numbers
- ☐ Biometric identifiers, including fingerprints and voice prints
- ☐ Full face photographic images and any comparable images
- ☐ Other unique identifying number, characteristic, or code (except a re-identification code)

If Other, explain:

Please clearly describe all PHI elements that will be shared outside Geisinger and to whom (such as, FDA, sponsor, other sites, collaborators, etc.)?

EHR data from study 2013-0322 will be used as part of this study. The PHI that is part of the EHR data will be shared with Johns Hopkins collaborators (under direction of Brian Schwartz) thru the already approved MOU/BAA to share data.

PHI may only be used or disclosed for research purposes under one or more of the following circumstances:

i. Written HIPAA Authorization
ii. Data Use Agreement (DUA) for the use of a limited data set
iii. Agreement for Disclosure of PHI to another institution
iv. Clinical trial or sponsored research agreement or sub-award

Waiver/Alteration of Authorization
i. Data Use Agreement (DUA) for the use of a limited data set
ii. Agreement for Disclosure of PHI to another institution

5.17 Are you requesting a Waiver of Authorization for the entire study?

○ Yes ◉ No

6.0 SRC Review

6.1 Is this research study investigator initiated?

◉ Yes ○ No

Investigator-initiated research includes any clinical trial or research study whose protocol was developed or idea was initiated by an investigator.

An investigator-initiated trial becomes a sponsor-investigator trial when the investigator obtains an IND.

6.2 Is there a therapeutic intent to the research study?

○ Yes ◉ No

Therapeutic intent means a specific endpoint sought in a line of therapeutic research – eg, prolongation of life, shrinkage of tumor, or improved quality of life, even in absence of cure or dramatic improvement of a condition." **or**

"When a major objective of the study seeks as its goal the diagnosis or treatment of disease including the observation of benefit of the intervention under study."

6.3 Has the research study had a previous peer review outside of Geisinger?

○ Yes ◉ No

Peer review is an assessment of the research protocol in order to maintain or enhance the quality of the work by people who are experts in the field under study.

6.4 Has the research study been reviewed by Geisinger's Scientific Review Committee (SRC)?

PLEASE NOTE: SRC review and positive outcome ("meritorius" ranking) are required for all investigator-initiated, greater than minimal risk studies that have not had an external scientific review (e.g., industry-sponsor, cooperative group, NIH, FDA, PCORI, etc.). The SRC determination

letter and critique must be submitted to the IRB with this study application. Attach SRC documents in *Study Documents* section.

○ Yes ◉ No

◉ Not applicable

7.0 Written Consent

7.1 Describe the setting and conditions under which consent/assent will be obtained, including parental permission or surrogate permission and the steps taken to ensure subjects' independent decision-making.

Consent will be obtained via mail. Patients will be identified based on questionnaire responses, and invited via letter to participate in the study. The consent packet including a short symptoms survey will be mailed to the potential participants home. If the participant returns a signed consent they will be contacted via phone and an appointment will be scheduled. If participants do not mail back a consent based on the first mailed contact, they will receive a phone call asking them if they are interested in participating and if needed a consent packet will be re-mailed to them.

7.2 List all personnel who will be involved in the consent process, which includes the consent interview, etc.

7.3 Describe the waiting period between informing the prospective participant and obtaining consent?

If none, please provide justification.

7.4 Specify the documents that will be used during the consent/assent process. Copies of all documents should be appended to the protocol, in the same format that they will be given to subjects.

An introductory letter, consent form, consent information sheet and short symptom survey will be mailed to the participant. See attached documents.

7.5 Explain provisions in place to ensure comprehension for research involving non-English speaking subjects. Translated copies of all consent materials must be submitted for approval prior to use.

We are currently not recruiting non-English speaking subjects. If we find we have many interested participants at a later date we will determine if it is in the best interest to translate the forms for use.

7.6 Indicate how the personnel obtaining consent will assess the potential subject's ability and capacity to consent to the research being proposed.

The ability to fill out the study consent paperwork and return, will show you the capacity to consent. Als all of the call center interviewers will be made aware in their study training to notify the study team about any participant responses that would call to question their ability to continue to consent to participate in the study if specifically applicable to our study.

8.0 Request for Partial Waiver of Authorization for Recruitment

8.1 *Complete this appendix to request a partial waiver of authorization for recruitment purposes.*

In the main application you indicated the PHI that will be collected as part of this research protocol. Please answer the following questions:

8.2 Explain how the use and disclosure of the information presents no more than minimal risk to the privacy of the individual?

We are requesting data that already exists in the EHR. As described in section 8.3, we will be taking multiple steps to protect confidentiality.

8.3 Describe the plan to protect the identifiers from improper use and disclosure (i.e., where will the identifiers will be stored and who will have access.)

Identifiers from the EHR will be stored in a password protected database on a Geisinger server, accessible only to IRB approved study staff. Consent form packets that patient name/address for mailing purposes will only be linked to a randomly generated study ID once it is scanned and stored in the study database. The paper consent will be stored in a locked file cabinent.

CT scan images will be de-identified with a random number at time of scan. The link between the study ID and identifiers from the EHR will be stored in a separate file that is password protected and accessible only to IRB approved study staff.

8.4 Describe the plan to destroy the identifiers at the earliest opportunity consistent with the conduct of the research. If there is a health or research justification for retaining identifiers or if such retention is required by law, please provide this information as well.

Data will be kept for an indefinite period of time for IRB-approved use in future studies.

8.5 Explain why the research could not be practicably conducted without the alteration or waiver.

This is a sub-study of a larger CRS analysis and questionnaire study (2013-0322). Based on analysis and questionnaire data we will identify patients that would qualify for CT scans. Without the ability to identify patients from the previous study that qualify we would be sending consent forms to many participants that would not meet the qualifications unnecessarily.

8.6 Explain why the research could not be conducted without access to and use of the PHI.

We need name and address fields to mail consent packets, as well as phone numbers to contact participants for recruitment.

Validation of a Questionnaire to Identify Patients with Chronic Rhinosinusitis

Initial Version:	January 27, 2014
Updated	May 5, 2014
Updated	June 17, 2014
Updated	June 28, 2014
Updated	February 4, 2015
Updated	March 26, 2015
Updated	September 1, 2016

Principal Investigator:
Name: Brian Schwartz, MD, MS
Address: Johns Hopkins University Bloomberg School of Public Health
Baltimore, MD
Telephone: 410-955-4158

Sub-Investigator(s):
Name: Annemarie Hirsch, PhD, MPH
Address: Geisinger Center for Health Research,
Danville, PA
Telephone: 570-214-4880

Geisinger Institutional Review Board (GIRB)
Geisinger Medical Center
100 N. Academy Avenue
Danville, PA 17822-3069
570-271-8663Tel

Geisinger

Approval Notice – Expedited Continuing Review

February 13, 2019

Brian S Schwartz, MD, MS
GMC - Center for Health Research

IRB #: **2014-0136 (CRS CT Validation)**, entitled ***Validation of a Questionnaire to Identify Patients with Chronic Rhinosinusitis***

RE: Geisinger Continuing Review Form, 02/01/2019 12:10:08 PM EST

Dear Brian S Schwartz, MD, MS:

The continuing review for the above study was reviewed and approved via expedited review Category 8(a): Continuing review of research previously approved by the convened IRB where (i) the research is permanently closed to the enrollment of new subjects; (ii) all subjects have completed all research-related interventions; and (iii) the research remains active only for long-term follow-up of subjects on 02/12/2019.

Please note the following information about your IRB approval:

Submission Components		
Form Name	Version	Outcome
Geisinger Continuing Review Form	Version 5.0	Approve

"HHS Final Rule" Transition Note - Geisinger IRB determined the following about this study:

- No further continuing review submission is required because the only remaining research activity is data analysis, including analysis of identifiable private information or identifiable biospecimens and qualifies to transition to HHS Final Rule continuing review requirements.
- All other IRB reporting requirements remain the same (e.g., amendments, study personnel changes, prompt reports of unanticipated problems and non-compliance).
- Submit a "Final Report" once the study is completed – see *Guidance – Study Closure*.

Geisinger

If you have any questions or need further help, please contact the Human Research Protection Program staff at (570) 271-8663.

Sincerely,

H. Lester Kirchner PhD
IRB Co-Chair
Institutional Review Board

William E. Crowder, Jr, MD FACOG
IRB Co-Chair
Institutional Review Board

cc: Dione G Mercer

Jordan Kuiper, M.S.

C: (763)-350-8617

E: jkuiper1@jhmi.edu
jkuiper91@live.com

A: 24 Breton Hill RD, 2B
Pikesville, MD 21208

Education

Ph.D. Environmental Health and Engineering, Johns Hopkins Bloomberg School of Public Health (*expected August 2019-May 2020*; *exact date depending on appropriate fit of available postdoctoral fellowships)*

Focus areas: environmental epidemiology; biostatistics; chronic rhinosinusitis

M.S. Cell and Molecular Biology, St. Cloud State University

Focus areas: cell and molecular biology; immunology; heavy metals; endocrine disrupting compounds; type 1 diabetes

B.E.S. Biology (Bachelor of Elective Studies), St. Cloud State University

Focus areas: evolution; microbiology; molecular biology

Research Experience

Doctoral Candidate, Johns Hopkins Bloomberg School of Public Health (JHSPH)

Department of Environmental Health and Engineering, Advisor: Brian S. Schwartz, M.D., M.S.

Developed expertise in:

- Causal inference, selection bias adjustment, survey methods
- Structural equation modeling/latent variable mixture modeling
    - Latent class analysis, exploratory and confirmatory factor analysis, Bayesian and exploratory structural equation modeling, finite mixture modeling
- Measurement theory (including item response theory)
- Machine learning (applied to prediction modeling)
    - Elastic net, LASSO, and ridge regression

- Random forest, classification tree, hierarchical k-cluster

Master's Student, St. Cloud State University (SCSU)

Department of Biology, Advisor: Marina Cetkovic-Cvrlje

Developed expertise in:

- Cell culturing
- Flow cytometry
- Immunotoxicology/immunology
- *in vivo* models of disease
- Cytokine profiling

Technical Expertise

Statistical Programming: Advanced command of Mplus and Stata; proficient in R.

- Muthén LK and Muthén BO, (1998-2018). **Mplus** User's Guide. Eighth Edition. Los Angeles, CA.
- R Development Core Team (2008). **R**: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. http://www.R-project.org.
- StataCorp. 2017. **Stata** Statistical Software: Release 15. College Station, TX: StataCorp LLC

Publications and Presentations

Publications:

- **Kuiper JR**, Hirsch AG, Bandeen-Roche K, et al. 2019. A new approach to categorization of radiologic inflammation in chronic rhinosinusitis. JACI. [*Submitted*]
- **Kuiper JR**, Hirsch AG, Bandeen-Roche K, et al. 2019. Workplace indirect cost impacts of nasal and sinus symptoms and related conditions. JOEM. [*published ahead of print*]. Doi: 10.1097/jom.0000000000001636.

- Cole M, Bandeen-Roche K, Hirsch AG, **Kuiper JR**, et al. 2018. Longitudinal evaluation of clustering of chronic sinonasal and related symptoms using exploratory factor analysis. Allergy, 73(8):1715-1723.
- **Kuiper JR**, Hirsch AG, Bandeen-Roche K, et al. 2018. Prevalence, severity, and risk factors for acute exacerbations of nasal and sinus symptoms by chronic rhinosinusitis status. Allergy, 73(6):1244-1253.
- **Kuiper JR**, Moran M, Cetkovic-Cvrlje M. 2016. Exposure to polychlorinated biphenyl-153 decreases incidence of autoimmune Type 1 diabetes in non-obese diabetic mice. J Immunotoxicol, 13(6):850-860.

Oral Presentations:

- **Kuiper JR**, Cetkovic-Cvrlje M. Polychlorinated biphenyl-153 and incidence of type 1 diabetes. April 2015. St. Cloud State University Student Research Colloquium.
- **Kuiper JR**, Cetkovic-Cvrlje M. Polychlorinated biphenyl-153: a risk factor for type 1 diabetes? April 2014. St. Cloud State University Student Research Colloquium.

Poster Presentations:

- **Kuiper JR**, Hirsch AG, Bandeen-Roche K, et al. Jan 2019. Chronic rhinosinusitis and other risk factors for workplace absenteeism and presenteeism. Environmental Health and Engineering Annual Research Retreat. Baltimore, MD.
- **Kuiper JR**, Hirsch AG, Bandeen-Roche K, et al. June 2018. Nasal and sinus symptoms: chronic rhinosinusitis and other risk factors for workplace absenteeism and presenteeism. Society for Epidemiologic Research. Baltimore, MD.
- **Kuiper JR**, Hirsch AG, Bandeen-Roche K, et al. Jan 2018. Prevalence, severity, and risk factors of acute exacerbations of nasal and sinus symptoms by chronic rhinosinusitis status. Environmental Health and Engineering Annual Research Retreat. Baltimore, MD.

Teaching Experience and Seminars

Co-Instructor: Lecture (University, Class, Year)

- Health impacts of the built environment: the role of metrics (JHSPH, A built environment for a healthy and sustainable future, 2017 & 2018).
- The built environment: a role for health impacts analysis? (JHSPH, A built environment for a healthy and sustainable future, 2017 & 2018).

- Epidemiology: the basic sciences of public health (SCSU, Public health controversies, 2014).
- Epidemiology: principles and methods (SCSU, Public health controversies, 2014).
- Problems and limits of epidemiology (SCSU, Public health controversies, 2014).
- Statistics: making sense of uncertainty (SCSU, Public health controversies, 2014).
- The role of data in public health (SCSU, Public health controversies, 2014).
- A clean environment: the basis of public health (SCSU, Public health controversies, 2014).
- Clean air: is it safe to breath? (SCSU, Public health controversies, 2014).
- Solid and hazardous wastes What to do with the garbage? (SCSU, Public health controversies, 2014).
- Clean water: a limited resource (SCSU, Public health controversies, 2014).
- Safe food and drugs: an ongoing regulatory battle (SCSU, Public health controversies, 2014).
- Population: the ultimate environmental health issue (SCSU, Public health controversies, 2014).

Guest Lecturer:

- The coming era of “tough” energy (JHSPH, Global environment, climate change, and public health, 2018).
- The built environment and public health (JHSPH, Global environment, climate change, and public health, 2018).
- Measuring sustainability (JHSPH, Global environment, climate change, and public health, 2018).
- Built environment-responses (JHSPH, Global environment, climate change, and public health, 2018).
- Nasal and sinus symptoms: understand chronic rhinosinusitis (JHSPH, Environmental health & engineering seminar, 2018).
- Acute exacerbation of nasal & sinus symptoms (JHSPH, Environmental health & engineering seminar, 2016).
- Epidemiology: biologists in public health. (SCSU, Biology department seminar, 2018)

Teaching Assistant:

- Global environmental sustainability and health seminar (JHSPH: Spring & Fall 2017; Spring & Fall 2018).

- Climate change and public health (JHSPH: Spring & Summer 2017; Summer 2018).
- A built environment for a healthy and sustainable future (JHSPH: Spring 2017; Spring 2018).
- Environmental health (JHSPH: Summer 2016; Summer 2017; Summer 2018).
- Cell function and inheritance (SCSU: Fall 2013; Spring, Summer, & Fall 2014; Spring & Summer 2015).

Accolades and Professional Development

Scholarships and Academic Honors:

- Funded Trainee, Johns Hopkins Education & Research Center for Occupational Safety & Health (2016 – Present)
- Distinguished thesis award, St. Cloud State University (2015)
- Best oral presentation, Student Research Colloquium, St. Cloud State University (2015)
- Runner-up best oral presentation, Student Research Colloquium, St. Cloud State University (2014)

Leadership Experience:

- Sustainability Coalition, Johns Hopkins Bloomberg School of Public Health – Inaugural Director (2018 – Present)
- Biology Graduate Student Association, St. Cloud State University – President (2014)
- St. Cloud State Immunology Lab – Manager (2013-2015)
